Oncology Reimagined: Treating Cancer Through Digital Twins

An Academic Reference Book for Physicians, Researchers, and Students

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List of Abbreviations

AI	Artificial Intelligence
CAR-T	Chimeric Antigen Receptor T-cell
CT	Computed Tomography
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DT	Digital Twin
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
IoT	Internet of Things
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PK/PD	Pharmacokinetic/Pharmacodynamic
TME	Tumor Microenvironment

VAF Variant Allele Frequency

Preface

The integration of digital innovation with medical practice has initiated a period of profound and far-reaching change in how healthcare is delivered. Among the most promising innovations emerging at this intersection is the concept of Digital Twins (DTs), computational models designed to replicate real-world physical entities by continuously incorporating data updates and running dynamic simulations. Although DT technology originated in aerospace and industrial engineering, it has proven particularly well-suited to biomedical contexts, particularly in the domain of oncology, where the complexity and heterogeneity of cancer demand highly individualized approaches to diagnosis and treatment.

This book, Oncology Reimagined: Treating Cancer Through Digital Twins, represents a comprehensive exploration of how DT technology is reshaping the landscape of cancer

care. The motivation for writing this text stems from the recognition that while the scientific literature on digital health technologies is expanding rapidly, there exists a significant gap in consolidated, academically rigorous resources that specifically address the application of DTs in oncology. Physicians, medical researchers, and students increasingly encounter references to DTs in journals and conferences, yet they lack a single reference that systematically covers the biological foundations, technical architecture, clinical applications, and ethical considerations of this transformative technology.

The book is structured to guide the reader from foundational concepts to advanced applications. The opening chapters establish the biological and technological groundwork, explaining cancer biology and the architecture of cancer DTs. Subsequent chapters delve into specific clinical applications, including diagnosis, personalized treatment planning, chemotherapy, immunotherapy, and radiation

oncology. Dedicated chapters address the critical issue of side effect prediction and mitigation, as well as the ethical, legal, and regulatory challenges that must be resolved before DTs can achieve widespread clinical adoption. The final chapter looks ahead to emerging technologies that will further enhance the capabilities of cancer DTs.

It is the hope of the author that this work will serve as both a scholarly reference and a practical guide, inspiring clinicians and researchers to engage with DT technology and contribute to its maturation. The potential of DTs to reduce the trial-and-error approach in cancer treatment, to predict adverse outcomes before they occur, and to democratize access to personalized medicine is immense. Realizing this potential will require sustained collaboration across disciplines, rigorous validation in clinical settings, and thoughtful navigation of the ethical landscape. This book aims to provide the foundation for that journey.

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Abstract

Cancer remains one of the most complex and heterogeneous diseases confronting modern medicine, demanding treatment strategies that are precise, adaptive, and patient-specific. This book presents a comprehensive examination of Digital Twin (DT) technology as a transformative framework for reimagining oncological care. A Digital Twin—a dynamic computational replica of a physical system continuously updated through real-world data—offers oncology an unprecedented capacity to model individual tumor biology, simulate treatment outcomes, and optimize therapeutic decisions before clinical implementation.

The book progresses systematically from foundational principles to advanced clinical applications. Early chapters establish the biological underpinnings of cancer, including

tumor microenvironment dynamics, clonal heterogeneity, and metastatic mechanisms, alongside the technical architecture required to construct cancer DTs from multi-modal data sources such as genomics, proteomics, medical imaging, electronic health records, and wearable sensors. Subsequent chapters address specific therapeutic domains: personalized treatment planning, chemotherapy and targeted therapy optimization via pharmacokinetic/pharmacodynamic modeling, immunotherapy and CAR-T cell simulation, and adaptive radiation oncology. A dedicated chapter examines the use of DT simulation to predict and mitigate treatment-related toxicities, including cardiotoxicity, nephrotoxicity, and neurotoxicity, with direct implications for patient quality of life. The book further explores the ethical, legal, and regulatory landscape governing DT deployment in clinical settings, and concludes with emerging frontiers including quantum computing integration, real-time IoT-enabled

twins, multi-patient population modeling, and CRISPR-guided gene therapy planning.

Intended for physicians, researchers, and students in oncology and biomedical informatics, this reference aims to bridge the gap between rapidly evolving digital health literature and consolidated clinical knowledge, providing both the theoretical grounding and practical perspective necessary to engage with DT technology in cancer care.

Keywords: Digital Twin; Oncology; Personalized Medicine; Artificial Intelligence; Cancer Treatment; Computational Modeling; Precision Oncology; Machine Learning; Tumor Simulation; Treatment Optimization

Chapter 1: Introduction to Digital Twins in Medicine

The concept of the Digital Twin (DT) has emerged as one of the most transformative technological paradigms of the twenty-first century, offering unprecedented capabilities in modeling, simulation, and real-time monitoring of complex systems. In the context of medicine, and particularly in oncology, DT technology holds the promise of revolutionizing how diseases are understood, diagnosed, and treated. This chapter introduces the foundational concepts of DT technology, traces its evolution from industrial origins to biomedical applications, and articulates why oncology represents an ideal domain for DT implementation.

1.1 Definition and Evolution of Digital Twin Technology

A Digital Twin can be understood as a living computational replica of a physical entity — whether an object, process, or system — sustained through continuous integration of real-world data and deployed for simulation, analytical, and optimization purposes [1]. The concept was introduced by Michael Grieves at the University of Michigan in 2002 within the domain of Product Lifecycle Management [2]. In its foundational formulation, a DT comprised three interdependent elements: a physical counterpart in the real world, a corresponding virtual model, and the data pathways connecting the two. Although this three-part architecture remains central to contemporary DT design, each of its constituent elements has undergone considerable advancement in complexity and capability.

The evolution of DT technology can be delineated into three distinct phases. The first phase, spanning from the early 2000s to approximately 2010, was characterized by applications in aerospace and defense, where NASA was

among the earliest adopters of DT concepts, applying them to simulate spacecraft behavior and anticipate maintenance requirements [3]. The second phase, from 2010 to 2018, witnessed the expansion of DTs into manufacturing, energy, and urban planning, driven by advances in the Internet of Things (IoT), cloud computing, and sensor technology [4]. The third and current phase, beginning around 2018, has seen the migration of DT concepts into healthcare and biomedicine, catalyzed by the exponential growth of health data, advances in artificial intelligence (AI), and the increasing demand for personalized medicine [5].

In the medical context, the definition of a DT has been refined to emphasize its role as a computational model that integrates multi-scale patient data to simulate physiological and pathological processes, predict disease trajectories, and optimize therapeutic interventions [6]. Unlike conventional computational models, which are typically static and population-based, medical DTs are inherently dynamic,

patient-specific, and designed for continuous learning and adaptation. This distinction is critical for understanding the unique value proposition of DTs in healthcare, as they enable a shift from reactive to proactive and predictive clinical decision-making [7].

1.2 From Industrial Origins to Biomedical Applications

The transition of DT technology from industrial to biomedical domains was neither immediate nor straightforward. In industrial settings, DTs benefit from well-characterized physical systems governed by deterministic laws, where sensor data can be collected with high precision and models can be validated against measurable outcomes [8]. In contrast, biological systems are inherently stochastic, characterized by non-linear dynamics, emergent properties, and individual variability that challenge conventional modeling approaches [9]. Despite

these challenges, several factors converged to make the biomedical application of DTs both feasible and compelling.

First, the proliferation of high-throughput omics technologies, including genomics, proteomics, and metabolomics, has generated vast quantities of patient-specific molecular data that can serve as inputs for DT construction [10]. Second, advances in medical imaging, particularly in functional and molecular imaging modalities such as PET-CT and MRI, have enabled the detailed characterization of tumor anatomy, physiology, and metabolism at the individual level [11]. Third, the widespread adoption of Electronic Health Records (EHRs) has created rich longitudinal datasets documenting patient histories, treatment regimens, and clinical outcomes that are essential for DT calibration and validation [12]. Fourth, advances in AI methodologies — particularly deep learning architectures and reinforcement learning frameworks — have equipped researchers with the analytical power to

identify meaningful signals within high-dimensional biomedical datasets and construct predictive models capable of characterizing disease progression [13].

The first biomedical DT applications emerged in the cardiovascular domain, where researchers at the University of Michigan developed patient-specific models of heart function for surgical planning [14]. Similar applications followed in musculoskeletal modeling, where DTs were used to simulate joint biomechanics and optimize orthopedic interventions [15]. However, it is in oncology that DT technology has found its most compelling and rapidly expanding application, driven by the unique characteristics of cancer as a disease that demands precise, individualized, and adaptive therapeutic strategies [16].

1.3 Key Components: Data Acquisition, Modeling, Simulation, and Feedback Loop

The architecture of a medical DT comprises four interconnected components that function in a continuous feedback loop. The first component is data acquisition, which involves the aggregation and harmonization of diverse patient-derived data streams — spanning genomic profiling, radiological imaging, laboratory diagnostics, wearable device outputs, and longitudinal clinical documentation [17]. The quality, granularity, and timeliness of input data are fundamental determinants of DT accuracy and utility. Modern DT systems employ automated data pipelines that standardize, annotate, and harmonize data from disparate sources to ensure consistency and interoperability [18].

The second component is computational modeling, which translates the integrated data into mathematical and statistical representations of the patient's physiological and pathological state. These models span multiple scales, from molecular networks and cellular interactions to tissue-level

dynamics and organ-level function [19]. Mechanistic models based on differential equations capture known biological processes, while data-driven models based on machine learning identify patterns and correlations that may not be apparent from first principles. The most effective DTs combine both approaches in hybrid models that leverage the strengths of each paradigm [20].

The third component is simulation, which uses the computational model to predict future states, test hypothetical interventions, and explore alternative treatment scenarios. Simulation enables clinicians to conduct in silico experiments that would be impractical, unethical, or impossible in real patients, such as comparing the expected outcomes of different chemotherapy regimens or predicting the long-term effects of radiation exposure on healthy tissues [21]. The fourth component is the feedback loop, which continuously updates the DT model with new patient data, refines model parameters, and improves prediction accuracy

over time. This iterative learning process is what distinguishes a DT from a static model and enables it to adapt to the evolving disease landscape of each individual patient [22].

1.4 Why Oncology Is an Ideal Field for DT Application

Oncology is uniquely suited for DT application for several compelling reasons. Cancer is a disease of extraordinary complexity, characterized by genetic heterogeneity, dynamic evolution, and intricate interactions between tumor cells and their microenvironment [23]. The traditional approach to cancer treatment, which relies on population-level evidence from clinical trials to guide therapy selection, often fails to account for the individual variability that determines treatment response and toxicity [24]. This one-size-fits-all paradigm results in significant overtreatment, undertreatment, and avoidable adverse effects, with

estimates suggesting that only approximately 25 percent of cancer patients receive the optimal first-line therapy based on current standard-of-care approaches [25].

DT technology addresses this limitation by enabling truly personalized cancer care. A cancer DT can integrate a patient's genomic profile, tumor histology, imaging characteristics, and clinical history to create a virtual replica that captures the unique biology of their disease [26]. This virtual replica can then be subjected to in silico testing of multiple therapeutic options, allowing clinicians to predict which treatments are most likely to be effective and which are likely to cause significant toxicity, before any drug is administered to the patient [27]. Furthermore, the dynamic nature of cancer, with its clonal evolution and acquired resistance mechanisms, makes the continuous monitoring and adaptation capability of DTs particularly valuable for managing treatment over time [28].

The economic burden of cancer care also motivates the adoption of DT technology. The global cost of cancer treatment exceeded 1.8 trillion USD in 2020, with a substantial portion attributable to ineffective first-line therapies and the management of treatment-related complications [29]. By improving treatment selection and reducing adverse events, DTs have the potential to generate significant cost savings while simultaneously improving patient outcomes, creating a compelling value proposition for healthcare systems, payers, and patients alike [30].

1.5 Current Landscape and Future Potential

The current landscape of DT applications in oncology is characterized by rapid growth, interdisciplinary collaboration, and increasing clinical validation. Several prominent research initiatives have demonstrated proof-of-concept DT systems for specific cancer types, including breast cancer, lung cancer, glioblastoma, and colorectal

cancer [31]. The European Commission has funded multiple large-scale projects, such as the DT4Oncology initiative, aimed at developing clinically deployable cancer DTs [32]. In the United States, the National Cancer Institute has identified DT technology as a priority area for research investment, recognizing its potential to accelerate the translation of precision oncology from bench to bedside [33].

Looking ahead, the future potential of cancer DTs is vast. Integration with emerging technologies such as quantum computing promises to dramatically accelerate simulation speed and model complexity, enabling real-time DT updates and predictions [34]. Advances in wearable and implantable sensors will provide continuous physiological data streams that further enhance DT fidelity and timeliness [35]. Perhaps most importantly, the development of population-level DTs that aggregate insights from thousands of individual patient twins could transform clinical trial design, drug

development, and population health management [36]. The remainder of this book provides a detailed exploration of the scientific foundations, technical architectures, clinical applications, and future directions of this transformative technology.

This chapter has established the conceptual and historical foundations of DT technology and articulated the rationale for its application in oncology. The following chapter examines the biological complexities of cancer that necessitate such personalized approaches.

Chapter 2: Biological Foundations of Cancer

Understanding the biological underpinnings of cancer is essential for appreciating why Digital Twin technology offers such transformative potential in oncology. Cancer is not a single disease but a collection of over 200 distinct

malignancies, each characterized by dysregulated cell proliferation, evasion of growth suppressors, and the capacity for tissue invasion and metastasis. This chapter provides a comprehensive overview of cancer biology, emphasizing the features that make the disease particularly amenable to DT-based modeling and simulation.

2.1 Cancer Hallmarks and Molecular Pathways

The conceptual framework of cancer hallmarks, originally proposed by Hanahan and Weinberg in 2000 and updated in 2011, identifies the fundamental capabilities that cells acquire during multistep tumor development [37]. Among the capabilities acquired by tumor cells are the maintenance of aberrant proliferative signals, circumvention of growth-inhibitory mechanisms, escape from programmed cell death, acquisition of unlimited replicative potential, stimulation of new blood vessel formation, and the capacity for local

invasion and systemic spread. A subsequent revision to this framework incorporated two additional emergent hallmarks — metabolic reprogramming and immune evasion — alongside two facilitating features: genomic instability coupled with mutational accumulation, and chronic inflammatory signaling that supports tumor progression [38].

Each hallmark is driven by specific molecular pathways that have been extensively characterized through decades of research. The MAPK/ERK and PI3K/AKT/mTOR pathways, for example, are central regulators of cell proliferation and survival, and their constitutive activation through mutations in genes such as KRAS, BRAF, and PIK3CA is observed across numerous cancer types [39]. The p53 tumor suppressor pathway, which governs cell cycle arrest, senescence, and apoptosis in response to DNA damage, is mutated in approximately 50 percent of all human cancers, making it the most frequently altered gene in

oncology [40]. The Wnt/beta-catenin pathway, critical for embryonic development and tissue homeostasis, is aberrantly activated in colorectal cancer, hepatocellular carcinoma, and other malignancies [41].

From a DT perspective, these molecular pathways represent the mechanistic backbone upon which computational models can be constructed. By encoding the known dynamics of signaling cascades into mathematical models, DTs can simulate how perturbations, whether caused by mutations or therapeutic interventions, propagate through cellular networks and alter phenotypic outcomes [42]. The integration of pathway-level modeling with patient-specific genomic data enables DTs to predict which pathways are driving an individual patient's tumor and, consequently, which targeted therapies are most likely to be effective [43].

2.2 Tumor Microenvironment

The Tumor Microenvironment (TME) encompasses the complex ecosystem of cellular and acellular components that surround and interact with tumor cells, including cancer-associated fibroblasts, immune cells, endothelial cells, pericytes, and the extracellular matrix [44]. Once considered a passive bystander in cancer progression, the TME is now recognized as an active participant in virtually every stage of carcinogenesis, from initiation through metastasis [45]. The dynamic crosstalk between tumor cells and their microenvironment influences therapeutic response, immune evasion, and the development of treatment resistance, making it a critical consideration for DT construction.

Immune cells within the TME play a particularly important role in shaping disease trajectory. Tumor-infiltrating lymphocytes, including cytotoxic CD8+ T cells and helper CD4+ T cells, can mediate tumor cell killing and are associated with favorable prognosis in many cancer types [46]. Conversely, regulatory T cells, tumor-associated

macrophages, and myeloid-derived suppressor cells create an immunosuppressive milieu that inhibits anti-tumor immunity and promotes disease progression [47]. The balance between pro-inflammatory and anti-inflammatory signals within the TME determines whether the immune response is effective in controlling tumor growth or is co-opted to support tumor survival and dissemination [48].

For DT applications, modeling the TME presents both opportunities and challenges. The spatial heterogeneity of the TME, with distinct immune niches existing within the same tumor, requires high-resolution spatial data, such as that provided by multiplex immunohistochemistry and spatial transcriptomics, to accurately reconstruct the microenvironmental landscape [49]. Agent-based models, which simulate the behavior of individual cells as autonomous agents following defined rules of interaction, have emerged as a powerful approach for capturing the emergent properties of the TME and predicting how

therapeutic interventions will alter the balance of forces within the tumor ecosystem [50].

2.3 Cancer Heterogeneity and Clonal Evolution

Within a single neoplasm, the coexistence of cancer cell populations that differ at both the genetic and phenotypic level constitutes intratumoral heterogeneity, whereas variation in tumors sharing the same histological classification across different individuals defines intertumoral heterogeneity [51]. Both phenomena are products of clonal evolutionary dynamics, through which successive mutational events generate divergent cellular lineages that are subsequently shaped by environmental selection pressures and the constraints imposed by therapeutic exposure [52]. The result is a constantly shifting landscape of clonal populations, with resistant clones expanding under therapeutic pressure and sensitive clones

declining, leading to treatment failure and disease progression.

Genomic studies have revealed that intratumoral heterogeneity is far more extensive than previously appreciated. Single-cell sequencing studies have demonstrated that individual tumors can harbor hundreds of distinct subclones, each with unique mutational profiles and functional properties [53]. This heterogeneity has profound implications for treatment, as therapies targeting a dominant clone may be ineffective against minor subclones that can subsequently repopulate the tumor [54]. Moreover, spatial heterogeneity, with different genomic alterations present in different regions of the same tumor, means that a single biopsy may not capture the full genomic landscape of the disease, potentially leading to incomplete or inaccurate therapeutic decisions [55].

DT technology is uniquely positioned to address the challenge of cancer heterogeneity. By integrating multi-

region sequencing data, circulating tumor DNA analysis, and serial imaging, a cancer DT can construct a comprehensive map of clonal diversity and track clonal dynamics over time [56]. Computational models of clonal evolution, based on evolutionary game theory and population genetics, can predict how clonal composition will change in response to different therapeutic pressures, enabling the design of adaptive treatment strategies that anticipate and pre-empt the emergence of resistance [57].

2.4 Metastasis Mechanisms

The dissemination of malignant cells from their site of origin to distant anatomical locations accounts for roughly 90 percent of cancer mortality and constitutes the principal obstacle confronting oncological practice [58]. This dissemination proceeds through an ordered sequence of biological events: initial infiltration of surrounding tissue, entry into vascular or lymphatic channels, persistence within

the circulatory environment, adhesion and penetration at remote sites, and ultimate establishment of secondary tumors in target organs [59]. Each step is regulated by complex molecular programs and interactions with the microenvironment, and only a tiny fraction of disseminated tumor cells successfully complete the entire cascade to form clinically detectable metastases [60].

Recent research has revealed that metastasis is not merely a late-stage phenomenon but can occur early in tumor development, with disseminated tumor cells often detected in bone marrow and circulating blood years before clinical diagnosis of metastatic disease [61]. The concept of pre-metastatic niches, whereby primary tumors remodel distant microenvironments to create favorable conditions for future colonization, has further transformed the understanding of the metastatic process [62]. These insights underscore the need for dynamic, systems-level approaches that can model the complex interplay between primary tumors, circulating

tumor cells, and distant organ microenvironments, precisely the capabilities that DTs are designed to provide [63].

2.5 Why Cancer Complexity Demands Personalized Approaches

The extraordinary complexity of cancer, arising from the convergence of genomic instability, clonal evolution, microenvironmental interactions, and metastatic dissemination, fundamentally precludes a uniform approach to treatment. Population-level clinical trials, the cornerstone of evidence-based oncology, provide statistical averages that may not apply to individual patients whose tumors harbor unique combinations of mutations, immune profiles, and microenvironmental contexts [64]. The frequent failure of first-line therapies and the development of resistance are direct consequences of this complexity, highlighting the urgent need for tools that can capture and reason about individual patient biology in all its nuance.

DT technology represents a paradigm shift from the current empiric approach to cancer treatment toward a rational, model-driven approach that accounts for the full complexity of each patient's disease [65]. By creating patient-specific virtual replicas that integrate multi-scale data and incorporate mechanistic models of cancer biology, DTs enable clinicians to simulate the likely consequences of therapeutic decisions before implementing them, to monitor disease evolution in real time, and to adapt treatment strategies dynamically in response to emerging resistance or changing clinical circumstances [66]. The following chapter examines the technical architecture that makes this vision possible.

This chapter has outlined the biological foundations that motivate the application of DT technology in oncology. The next chapter describes the architectural framework for constructing cancer DTs.

Chapter 3: Architecture of Cancer Digital Twins

The construction of a cancer Digital Twin requires a sophisticated computational architecture capable of integrating heterogeneous data sources, performing multi-scale modeling, executing real-time simulations, and delivering actionable clinical insights. This chapter provides a detailed examination of the architectural components that underpin cancer DTs, from data acquisition and processing to model construction and deployment.

3.1 Data Sources: Genomics, Proteomics, Imaging, EHR, and Wearables

The foundation of any cancer DT is the data that informs its construction and sustains its operation. Modern oncology generates an extraordinary volume and variety of patient

data, each source providing unique insights into different aspects of the disease [67]. Genomic data, derived from whole-exome sequencing, whole-genome sequencing, and targeted gene panels, reveal the mutational landscape of the tumor, identifying driver mutations, copy number alterations, and structural variants that inform therapeutic target selection [68]. Transcriptomic data from RNA sequencing provides information about gene expression programs that are active in the tumor, offering a functional readout that complements the structural information from DNA sequencing [69].

Proteomic and metabolomic data add further layers of biological insight, capturing the post-transcriptional and post-translational modifications that ultimately determine cellular behavior [70]. Medical imaging data, including CT, MRI, PET, and ultrasound, provide spatial and temporal information about tumor anatomy, physiology, and metabolism that is essential for treatment planning and

monitoring [71]. EHR data document the longitudinal clinical trajectory of the patient, including comorbidities, treatment history, laboratory values, and outcomes, providing the contextual framework within which molecular and imaging data must be interpreted [72]. Wearable and implantable sensors, an increasingly important data source, enable continuous monitoring of physiological parameters such as heart rate, activity levels, and sleep patterns, offering insights into patient well-being and treatment tolerance that are not captured by periodic clinical assessments [73].

The integration of these disparate data sources presents significant technical challenges related to data heterogeneity, quality, and interoperability. Data harmonization pipelines must standardize formats, reconcile conflicting measurements, and handle missing data while preserving the biological signal [74]. Ontology-based data integration frameworks, such as those built on the Observational Health Data Sciences and Informatics

(OHDSI) Common Data Model, provide structured approaches to harmonizing clinical data across institutions [75]. Federated learning architectures enable DT construction from distributed data sources without centralizing sensitive patient information, addressing both technical and privacy concerns [76].

3.2 Multi-Scale Modeling: Molecular to Cellular to Organ to Patient

Cancer is a multi-scale disease, with phenomena at the molecular level, such as mutations and signaling events, giving rise to cellular behaviors, such as proliferation and migration, that in turn manifest as tissue-level changes, such as tumor growth and invasion, ultimately producing patient-level symptoms and outcomes [77]. A cancer DT must therefore employ multi-scale modeling strategies that can capture phenomena across this entire spectrum and integrate them into a coherent computational framework [78].

Table 3.1: Comparison of Multi-Scale Modeling Approaches in Cancer Digital Twins

Scale	Modeling Approach	Key Data Inputs	Computational Cost
Molecular	Ordinary differential equations, Bayesian networks	Genomics, proteomics	Low to moderate
Cellular	Agent-based models, cellular automata	Single-cell data, imaging	Moderate to high
Tissue	Finite element analysis, continuum models	Imaging, histopathology	High
Organ	Physiological models, pharmacokinetic models	EHR, imaging, labs	Moderate

Scale	Modeling Approach	Key Data Inputs	Computational Cost
Patient	Machine learning, decision trees	Clinical data, outcomes	Low to moderate

Source: Adapted from multi-scale cancer modeling literature [77-80]

At the molecular scale, ordinary differential equation models and Bayesian networks capture the dynamics of signaling pathways and gene regulatory networks [79]. At the cellular scale, agent-based models simulate the behavior of individual cells as autonomous agents that interact with their neighbors and microenvironment according to biologically informed rules [80]. At the tissue scale, continuum models based on partial differential equations describe tumor growth, invasion, and response to therapy as continuous processes governed by physical and biological laws [81]. At the organ scale, pharmacokinetic and pharmacodynamic models describe the absorption, distribution, metabolism,

and excretion of therapeutic agents and their effects on tumor and normal tissues [82]. At the patient scale, machine learning models trained on clinical outcomes data provide predictions of treatment response, survival, and quality of life [83].

3.3 AI and Machine Learning Integration

Artificial intelligence and machine learning are indispensable components of the cancer DT architecture, providing the analytical capabilities necessary to extract patterns from high-dimensional data, make predictions about future disease states, and optimize treatment decisions [84]. Deep learning algorithms, particularly convolutional neural networks and transformer architectures, have demonstrated remarkable performance in analyzing medical images, identifying radiomic features associated with treatment response and prognosis, and detecting patterns in

histopathological data that are invisible to the human eye [85].

Reinforcement learning — a machine learning paradigm wherein a computational agent discovers optimal decision strategies by iteratively interacting with a simulated environment — offers particular promise for the challenge of dynamically optimizing cancer treatment regimens [86]. In the DT context, the reinforcement learning agent can interact with the virtual patient model, exploring different treatment strategies in silico and learning policies that maximize long-term outcomes such as progression-free survival while minimizing toxicity [87]. This approach has shown promising results in simulation studies for prostate cancer, lung cancer, and glioblastoma, although translation to clinical practice remains an active area of research [88].

Physics-informed neural networks constitute a recently developed computational approach that merges the pattern-recognition capabilities of deep learning with the structural

constraints imposed by known physical and biological principles [89]. By embedding known biological relationships, such as mass conservation and reaction kinetics, into the neural network architecture, these models achieve greater accuracy and generalizability than purely data-driven approaches, particularly in data-sparse regimes where training samples are limited [90]. This hybrid approach is especially relevant for cancer DTs, where the complexity of the underlying biology often exceeds the availability of training data.

3.4 Real-Time Data Synchronization

A defining feature of a DT, as distinct from a static computational model, is its capacity for real-time data synchronization, whereby the virtual replica is continuously updated with new data from the physical patient to maintain fidelity between the two [91]. In the cancer context, real-time synchronization involves the ingestion of streaming

data from wearable devices, periodic updates from laboratory tests and imaging studies, and event-driven updates from clinical encounters, all of which must be processed, validated, and incorporated into the DT model with minimal latency [92].

The technical infrastructure for real-time synchronization typically employs a lambda architecture, which combines a speed layer for processing real-time data streams with a batch layer for comprehensive historical analysis [93]. Apache Kafka and Apache Flink are commonly used for stream processing, while cloud-based data lakes provide scalable storage for the accumulated patient data [94]. Edge computing devices, deployed at the point of care or on the patient's body, can perform preliminary data processing and filtering to reduce bandwidth requirements and accelerate response times [95]. The challenge of data synchronization is compounded by the varying temporal resolution of different data sources, from continuous physiological

monitoring to weekly or monthly clinical assessments, requiring sophisticated temporal alignment and interpolation strategies [96].

3.5 Technical Infrastructure and Computational Requirements

The computational demands of cancer DTs are substantial, reflecting the complexity of the models, the volume of the data, and the requirement for real-time processing. High-performance computing clusters, equipped with graphics processing units for deep learning workloads and large-memory nodes for genomic analysis, form the backbone of the computational infrastructure [97]. Cloud computing platforms, such as Amazon Web Services, Microsoft Azure, and Google Cloud Platform, provide elastic scalability and access to specialized hardware, enabling DT systems to scale dynamically in response to varying computational loads [98].

Containerization technologies, particularly Docker and Kubernetes, facilitate the deployment and orchestration of DT components across distributed computing environments, ensuring reproducibility and portability [99]. The adoption of FAIR data principles, which mandate that data be Findable, Accessible, Interoperable, and Reusable, is essential for enabling DTs to leverage data from multiple institutions and to contribute to the broader research ecosystem [100]. Security and privacy infrastructure, including encryption, access control, and audit logging, must be embedded at every layer of the architecture to protect sensitive patient information and comply with regulatory requirements such as HIPAA and GDPR [101].

This chapter has described the architectural framework for cancer DTs. The following chapter examines how this architecture is applied to enhance cancer diagnosis.

Chapter 4: Digital Twins in Cancer Diagnosis

Early and accurate diagnosis is the cornerstone of effective cancer treatment, yet the diagnostic process in oncology remains fraught with uncertainty, subjectivity, and delay. Digital Twin technology offers transformative capabilities for enhancing cancer diagnosis by integrating multi-modal data, enabling virtual biopsies, and supporting differential diagnosis through computational reasoning. This chapter explores the application of DTs across the diagnostic continuum, from early detection to differential diagnosis.

4.1 Early Detection Enhancement via DT Simulation

Early detection of cancer significantly improves patient outcomes, with five-year survival rates for many cancers

exceeding 90 percent when the disease is diagnosed at an early localized stage compared to less than 20 percent for metastatic disease [102]. However, current screening programs, such as mammography for breast cancer and low-dose CT for lung cancer, are limited by imperfect sensitivity, false-positive results, and the inability to distinguish indolent tumors from aggressive ones that require immediate intervention [103]. DT technology can enhance early detection by integrating individual patient risk profiles with population-level epidemiological data to create personalized screening schedules that optimize the trade-off between detection benefit and overdiagnosis harm [104].

DT simulations can model the natural history of tumor growth from subclinical stages, incorporating individual risk factors such as genetic predisposition, lifestyle factors, and environmental exposures, to predict the likelihood and timing of cancer development in specific patients [105]. By simulating thousands of virtual patient trajectories, DTs can

identify the screening intervals and modalities that maximize the probability of detecting cancer at a treatable stage while minimizing unnecessary procedures [106]. Furthermore, DTs can incorporate real-time data from wearable sensors and blood-based biomarkers, such as circulating tumor DNA, to trigger diagnostic evaluations when subtle physiological changes suggest the emergence of an early malignancy, enabling a shift from periodic screening to continuous surveillance [107].

4.2 Imaging-Based DT Construction

Medical imaging is the primary modality for cancer diagnosis, staging, and treatment monitoring, and it serves as a critical data source for DT construction. CT, MRI, and PET provide complementary information about tumor anatomy, physiology, and metabolism that can be synthesized into a comprehensive virtual representation of the patient's disease [108]. Radiomics, the high-throughput

extraction of quantitative features from medical images, has identified imaging biomarkers that correlate with tumor genotype, prognosis, and treatment response, providing the feature space upon which DT models can be trained [109].

The construction of imaging-based DTs typically involves several steps. First, images are segmented to delineate tumor volumes and regions of interest using automated or semi-automated algorithms [110]. Second, radiomic features are extracted from the segmented regions, capturing properties such as texture, shape, and intensity heterogeneity that reflect underlying tumor biology [111]. Third, these features are combined with clinical and molecular data in machine learning models that predict clinically relevant endpoints, such as treatment response or risk of recurrence [112]. Fourth, the imaging-derived model is integrated into the broader DT framework, where it can be updated with new imaging data and used to simulate the effects of different

therapeutic interventions on tumor size, morphology, and metabolism [113].

4.3 Biomarker Integration and Liquid Biopsy Data

The integration of biomarker data into cancer DTs significantly enhances their diagnostic and prognostic capabilities. Tissue biomarkers, assessed through immunohistochemistry and molecular profiling of biopsy specimens, provide information about protein expression, gene amplification, and mutational status that guides therapy selection [114]. Liquid biopsy biomarkers, including circulating tumor DNA, circulating tumor cells, and exosomal microRNA, offer a minimally invasive window into tumor biology that can be sampled repeatedly over time, enabling longitudinal monitoring of clonal evolution and treatment response that is not feasible with tissue biopsies alone [115].

The incorporation of liquid biopsy data into DTs addresses a critical limitation of tissue-based diagnostics, which provide a static snapshot of a tumor at a single time point and may not capture the evolving genomic landscape of the disease [116]. Serial liquid biopsy sampling enables DTs to track changes in variant allele frequencies over time, detect the emergence of resistance mutations before clinical progression, and trigger early treatment modifications that pre-empt disease relapse [117]. Studies have demonstrated that circulating tumor DNA can detect minimal residual disease after curative-intent surgery months before radiographic recurrence, providing a window of opportunity for adjuvant therapy that might otherwise be missed [118].

4.4 Differential Diagnosis Support

Oncological differential diagnosis frequently requires clinicians to differentiate neoplastic from non-neoplastic lesions, determine histological tumor subtype, and trace the

anatomical origin of metastatic disease when the primary site remains unknown. These tasks require the synthesis of clinical, radiological, pathological, and molecular information and are often complicated by overlapping features and atypical presentations [119]. DT-based diagnostic support systems can augment clinical reasoning by comparing a patient's virtual profile against large databases of characterized cases, identifying the diagnostic categories most consistent with the observed data, and quantifying the uncertainty associated with each potential diagnosis [120].

Case-based reasoning — an established AI methodology in which novel diagnostic challenges are addressed by drawing on analogous cases encountered previously — aligns naturally with DT-assisted differential diagnosis workflows [121]. In this framework, the DT serves as the case representation, encoding the multi-modal features of the patient's disease in a structured format that enables

similarity-based retrieval from a case library. When a new patient's DT is constructed, the system identifies the most similar historical cases and presents their diagnoses and outcomes as evidence to support clinical decision-making, while also highlighting the features that distinguish the current case from its nearest neighbors [122].

4.5 Case-Based Reasoning with DT Models

The integration of case-based reasoning with DT models creates a powerful diagnostic platform that combines the strengths of both approaches. The DT provides a rich, multi-scale representation of the patient that captures the complexity of their disease, while case-based reasoning provides a transparent and interpretable mechanism for leveraging the collective experience encoded in historical cases [123]. Unlike purely data-driven machine learning approaches, which can function as black boxes, case-based reasoning provides explicit references to similar cases,

enabling clinicians to evaluate the relevance and applicability of the suggested diagnosis and to exercise their own clinical judgment [124].

Validation studies of DT-based diagnostic systems have demonstrated promising results in specific cancer types. A DT system for lung nodule classification achieved an area under the receiver operating characteristic curve of 0.92 in a multi-center validation study, outperforming both the Brock University cancer prediction model and the Mayo Clinic model [125]. Similarly, a DT-based system for breast cancer molecular subtype prediction from imaging data alone achieved concordance rates of 85 percent with immunohistochemistry-based classification, suggesting the potential for non-invasive virtual biopsies that could reduce the need for invasive tissue sampling [126]. These results, while encouraging, require further validation in larger, prospective clinical trials before DT-based diagnostic tools can be integrated into routine clinical practice [127].

This chapter has explored the application of DTs in cancer diagnosis. The next chapter examines how DTs are used to plan personalized treatment strategies.

Chapter 5: Personalized Treatment Planning Using Digital Twins

The translation of diagnostic information into an optimal treatment plan is one of the most consequential and challenging tasks in clinical oncology. Traditional treatment planning relies on population-level evidence from clinical trials, clinical guidelines, and physician experience, approaches that often fail to account for the unique biological characteristics and clinical circumstances of individual patients. Digital Twin technology enables a fundamentally different paradigm, in which treatment strategies are evaluated, optimized, and personalized

through in silico simulation before being implemented in the patient.

5.1 Simulating Treatment Outcomes Before Administration

The ability to simulate treatment outcomes before administration is perhaps the most transformative capability of cancer DTs. In the current clinical paradigm, treatment selection is essentially an experiment, with the patient serving as their own control and the outcome assessed retrospectively after the intervention has been delivered [128]. DT technology replaces this empiric approach with a rational, model-driven strategy in which multiple therapeutic options are tested on the virtual patient, and the predicted outcomes are compared to identify the optimal course of action [129]. This in silico experimentation is analogous to wind tunnel testing in aerospace engineering, where designs

are evaluated and refined virtually before physical prototypes are constructed [130].

The simulation of treatment outcomes requires the integration of multiple model components. Tumor growth models predict the effects of therapy on tumor burden, accounting for drug-specific mechanisms of action, dose-response relationships, and pharmacokinetic variability [131]. Toxicity models predict the effects of therapy on normal tissues, incorporating patient-specific risk factors such as age, comorbidities, and genetic polymorphisms affecting drug metabolism [132]. Resistance models predict the likelihood and timing of acquired resistance, based on the initial clonal composition of the tumor and the selective pressures imposed by the therapy [133]. By integrating these model components, the DT generates a comprehensive forecast of the treatment trajectory, including expected tumor response, time to progression, and probability of

adverse events, enabling a quantitative comparison of alternative treatment strategies [134].

5.2 Drug Selection and Dosage Optimization

Drug selection in oncology is increasingly guided by molecular profiling of the tumor, which identifies actionable genomic alterations that can be targeted with specific agents [135]. However, the presence of a targetable mutation does not guarantee response to the corresponding targeted therapy, as resistance mechanisms, pharmacokinetic variability, and drug-drug interactions can significantly modify treatment outcomes [136]. DTs address this limitation by simulating the pharmacokinetic and pharmacodynamic behavior of candidate drugs in the context of the patient's specific tumor biology and physiological characteristics [137].

Dosage optimization is another area where DTs offer significant advantages over current approaches. Standard

dosing regimens, based on body surface area or fixed doses derived from population pharmacokinetic studies, often result in subtherapeutic or supratherapeutic drug concentrations in individual patients, leading to treatment failure or excessive toxicity [138]. DT-based pharmacokinetic models can predict individual drug exposure based on patient-specific factors, including renal function, hepatic metabolism, body composition, and concomitant medications, and can recommend dose adjustments that achieve target drug concentrations while minimizing the risk of adverse events [139]. This approach is particularly valuable for drugs with narrow therapeutic indices, such as chemotherapeutic agents, where small deviations from optimal dosing can have significant clinical consequences [140].

5.3 Surgical Planning and Simulation

Surgical resection remains a cornerstone of curative-intent cancer treatment, yet surgical planning is often based on two-dimensional imaging studies that may not fully capture the three-dimensional anatomy of the tumor and its relationship to critical structures [141]. DT technology enables the construction of patient-specific three-dimensional anatomical models that can be manipulated, sectioned, and viewed from any angle, providing surgeons with an immersive understanding of the operative field before entering the operating room [142]. Virtual reality and augmented reality interfaces further enhance the utility of these models by allowing surgeons to rehearse the planned procedure in a realistic simulated environment [143].

Beyond anatomical visualization, DTs can simulate the physiological consequences of surgical interventions, predicting postoperative liver remnant volumes after hepatectomy, cardiac function after lung resection, and the hemodynamic consequences of vascular reconstruction

[144]. These simulations enable surgeons to assess the feasibility and safety of different surgical approaches, to identify patients at high risk for postoperative complications, and to design operative strategies that maximize tumor clearance while preserving organ function [145]. Intraoperatively, DT models can be overlaid on the surgical field through augmented reality displays, providing real-time navigation guidance that enhances the precision and safety of the procedure [146].

5.4 Radiation Therapy Planning

Radiation therapy planning is a computational intensive process that requires the precise calculation of radiation dose distributions within the patient's body to maximize tumor cell killing while minimizing damage to surrounding healthy tissues [147]. DT technology enhances conventional radiation therapy planning by incorporating patient-specific biological information, such as tumor radiosensitivity and

normal tissue tolerance, into the optimization process [148]. Radiobiological models, including the linear-quadratic model and its extensions, can be parameterized with patient-specific data to predict the probability of tumor control and normal tissue complications for different dose fractionation schemes [149].

Adaptive radiation therapy, in which the treatment plan is modified during the course of treatment in response to changes in tumor size, shape, and position, represents a natural application of DT technology [150]. By continuously updating the DT model with daily imaging data, the radiation plan can be re-optimized to account for anatomical changes, such as tumor shrinkage or weight loss, ensuring that the delivered dose remains consistent with the intended plan throughout the treatment course [151]. This adaptive approach has been shown to improve tumor control probabilities and reduce normal tissue complication

probabilities compared to conventional non-adaptive treatment delivery [152].

5.5 Reducing Trial-and-Error in Clinical Decision-Making

Current approaches to oncological treatment selection rely heavily on empirical iteration, with many patients progressing through successive therapeutic regimens before an effective option is identified — a process that delays optimal care, imposes avoidable toxic burden, and places considerable strain on healthcare resources [153]. DT technology has the potential to dramatically reduce this trial-and-error approach by enabling clinicians to predict which treatments are most likely to benefit an individual patient before any therapy is administered [154].

Retrospective studies have demonstrated the potential of DT-guided treatment selection to improve outcomes. A

study of DT-guided chemotherapy selection in ovarian cancer found that the DT-predicted optimal regimen achieved a response rate 23 percentage points higher than the standard-of-care regimen selected by physician choice [155]. Similarly, a DT-based decision support system for metastatic colorectal cancer demonstrated that treatment selections aligned with DT predictions correlated with meaningfully extended progression-free survival intervals relative to patients whose treating clinicians selected regimens inconsistent with DT-generated guidance [156]. While these retrospective findings are encouraging, prospective randomized trials are needed to definitively establish the clinical benefit of DT-guided treatment selection and to address concerns about model generalizability and validation [157].

This chapter has examined how DTs enable personalized treatment planning. The following chapters explore specific

applications of DTs in chemotherapy, immunotherapy, and radiation oncology.

Chapter 6: Digital Twins in Chemotherapy and Targeted Therapy

Chemotherapy and targeted therapy remain the pillars of systemic cancer treatment, yet their efficacy is limited by inter-patient variability in drug response, the development of resistance, and dose-limiting toxicities. Digital Twin technology offers a comprehensive framework for optimizing the use of these therapeutic modalities through pharmacokinetic and pharmacodynamic modeling, resistance prediction, combination therapy optimization, and toxicity minimization. This chapter provides a detailed examination of DT applications in chemotherapy and targeted therapy.

6.1 Pharmacokinetic/Pharmacodynamic Modeling

Pharmacokinetic/pharmacodynamic (PK/PD) modeling is the quantitative study of drug absorption, distribution, metabolism, excretion, and effect, and it forms the scientific foundation for rational dosing of chemotherapeutic and targeted agents [158]. Population PK/PD models, developed from clinical pharmacokinetic studies, describe the typical drug behavior in a patient population and the sources of inter-patient variability [159]. DT technology extends population PK/PD models by incorporating patient-specific data, including genotypic information about drug-metabolizing enzymes and transporters, organ function parameters, body composition metrics, and concomitant medication profiles, to generate individualized predictions of drug exposure and response [160].

The clinical impact of PK/PD-informed dose individualization has been demonstrated in several settings. For drugs with narrow therapeutic indices, such as the chemotherapeutic agents carboplatin and 5-fluorouracil, PK-guided dosing has been shown to reduce inter-patient variability in drug exposure and to improve treatment outcomes compared to body surface area-based dosing [161]. DT-based PK/PD models go beyond single-dose optimization by simulating the entire treatment course, accounting for changes in organ function over time, drug accumulation effects, and drug-drug interactions that emerge with multi-agent regimens [162]. This longitudinal perspective enables the design of adaptive dosing protocols that maintain optimal drug exposure throughout the treatment trajectory, even as the patient's physiological state evolves [163].

6.2 Predicting Drug Resistance

Drug resistance, whether intrinsic or acquired, is the primary cause of treatment failure in cancer chemotherapy and targeted therapy [164]. Intrinsic resistance refers to the pre-existing insensitivity of tumor cells to a therapeutic agent, often due to genetic alterations that activate alternative survival pathways or efflux drug molecules [165]. Acquired resistance develops during the course of treatment through the selection and expansion of resistant subclones, the activation of compensatory signaling pathways, or the acquisition of new mutations that circumvent the drug's mechanism of action [166].

DTs can predict drug resistance through several complementary mechanisms. First, by integrating the genomic profile of the tumor at baseline, DTs can identify known resistance mechanisms, such as KRAS mutations conferring resistance to EGFR inhibitors in colorectal cancer or T790M mutations conferring resistance to first-generation EGFR tyrosine kinase inhibitors in lung cancer, and flag

therapies that are unlikely to be effective [167]. Second, by modeling the clonal architecture of the tumor and simulating the selective pressures imposed by different therapies, DTs can predict the emergence of resistant clones and estimate the time to resistance [168]. Third, by incorporating serial liquid biopsy data, DTs can detect the early rise of resistance-associated mutations in circulating tumor DNA, enabling pre-emptive treatment modifications before clinical progression [169].

6.3 Combination Therapy Optimization

Combination therapy, the simultaneous or sequential administration of multiple therapeutic agents, is a mainstay of cancer treatment that aims to improve efficacy through synergistic or additive effects while delaying the emergence of resistance [170]. However, identifying optimal drug combinations from the vast space of possible combinations represents a formidable combinatorial challenge that

exceeds the capacity of traditional clinical trial methodologies [171]. DT technology enables systematic in silico screening of drug combinations, predicting synergistic, additive, or antagonistic interactions based on the known mechanisms of action of the drugs and the molecular characteristics of the tumor [172].

The optimization of combination therapy through DT simulation involves several steps. First, the tumor's dependency pathways are identified through genomic and transcriptomic analysis, revealing the signaling nodes that are most critical for tumor survival [173]. Second, candidate drug combinations targeting these dependency pathways are assembled, prioritizing combinations that simultaneously inhibit multiple essential pathways or that create synthetic lethality [174]. Third, the predicted effects of each combination are simulated using the DT, incorporating PK/PD interactions, dose scheduling considerations, and expected toxicity profiles [175]. Fourth, the simulation

results are ranked according to a composite efficacy-toxicity metric, and the top-ranked combinations are recommended for clinical evaluation [176].

6.4 Toxicity Prediction and Side Effect Minimization

Chemotherapy-induced toxicity remains a major source of morbidity and mortality in cancer patients, with grade 3 or higher adverse events occurring in 30 to 50 percent of patients receiving standard regimens [177]. The most common and clinically significant toxicities include myelosuppression, gastrointestinal toxicity, cardiotoxicity, nephrotoxicity, and neurotoxicity, each of which can necessitate dose reductions, treatment delays, or discontinuation of therapy, compromising the chances of treatment success [178]. DT-based toxicity prediction models integrate patient-specific risk factors, including age, comorbidities, genetic polymorphisms in drug metabolism

pathways, and baseline organ function, to predict the probability and severity of specific toxicities for individual patients [179].

Table 6.1: DT-Based Toxicity Prediction Models for Common Chemotherapy Agents

Chemotherapy Agent	Primary Toxicity	Key Risk Factors in DT Model	Prediction Accuracy (AUC)
Doxorubicin	Cardiotoxicity	Age, cumulative dose, baseline LVEF	0.85
Cisplatin	Nephrotoxicity	Baseline eGFR, hydration, age	0.82

Chemotherapy Agent	Primary Toxicity	Key Risk Factors in DT Model	Prediction Accuracy (AUC)
Paclitaxel	Neurotoxicity	Cumulative dose, diabetes, age	0.79
5-Fluorouracil	GI toxicity	DPD deficiency, dose, schedule	0.81
Oxaliplatin	Neurotoxicity	Cumulative dose, neuropathy history	0.77

Source: Compiled from DT toxicity prediction studies [179-183]

6.5 Adaptive Chemotherapy Protocols

Adaptive chemotherapy protocols represent a paradigm shift from the fixed-dose, fixed-schedule regimens that have

dominated oncology practice for decades [184]. In the adaptive paradigm, treatment decisions, including drug selection, dose, and schedule, are continuously adjusted in response to the patient's evolving clinical status, tumor response, and toxicity profile [185]. DT technology provides the computational infrastructure necessary to implement adaptive chemotherapy at scale, by continuously updating the patient's virtual replica with new clinical and laboratory data, re-simulating treatment trajectories under alternative dosing strategies, and recommending modifications that optimize the trade-off between efficacy and toxicity [186].

The mathematical foundation of adaptive chemotherapy draws on optimal control theory, evolutionary game theory, and reinforcement learning [187]. Evolutionary models of tumor response to therapy suggest that maintaining a stable population of treatment-sensitive cells can suppress the growth of resistant clones through competitive ecological interactions, a strategy known as adaptive therapy [188].

Clinical trials of adaptive therapy in metastatic prostate cancer and melanoma have demonstrated that this approach can significantly prolong time to treatment failure while using lower cumulative drug doses compared to maximum tolerated dose strategies [189]. DT-based adaptive protocols extend this concept by personalizing the adaptation strategy to the individual patient's clonal architecture and treatment response dynamics, enabling truly precision adaptive oncology [190].

This chapter has explored DT applications in chemotherapy and targeted therapy. The next chapter examines the role of DTs in immunotherapy and CAR-T cell therapy, where unique modeling challenges and opportunities arise.

Chapter 7: Digital Twins in Immunotherapy and CAR-T Cell Therapy

Immunotherapy has revolutionized cancer treatment, offering durable responses in a subset of patients across a range of malignancies. However, the unpredictability of immunotherapy response, the risk of severe immune-related adverse events, and the complexity of immune-tumor interactions present significant clinical challenges. Digital Twin technology provides a framework for modeling the immune-tumor interface, predicting treatment response, and personalizing immunotherapy strategies. This chapter examines DT applications in immune checkpoint inhibition, CAR-T cell therapy, and related immunotherapeutic modalities.

7.1 Modeling Immune-Tumor Interactions

The relationship between host immunity and tumor biology is neither static nor unidirectional; rather, it constitutes an ongoing, multidimensional interplay shaped by an intricate web of cellular signaling and molecular crosstalk [191]. To

persist within an immunologically active host, neoplastic cells exploit diverse evasion strategies — among them suppression of MHC surface expression, upregulation of checkpoint pathway ligands, elaboration of immunosuppressive mediators, and active recruitment of tolerance-promoting immune subsets [192]. In counterpoint, the immune system mobilizes an array of cytotoxic effector responses, engaging CD8+ T lymphocytes, NK cells, and antibody-mediated cytotoxic mechanisms in efforts to eliminate transformed cells [193]. The balance between these pro-tumor and anti-tumor forces determines whether the immune response is effective in controlling tumor growth or is subverted to support tumor progression [194].

DT models of immune-tumor interactions typically employ ordinary differential equation systems or agent-based models that represent the key cellular populations, including tumor cells, cytotoxic T lymphocytes, regulatory T cells, tumor-associated macrophages, and dendritic cells, and their

interactions through cytokines, checkpoint molecules, and antigen presentation [195]. These models can be parameterized with patient-specific data, including tumor mutational burden, neoantigen load, immune cell infiltration patterns from multiplex immunohistochemistry, and cytokine profiles from peripheral blood analysis, to create individualized representations of the immune-tumor interface [196]. The resulting DT can simulate how perturbations, such as checkpoint inhibition or adoptive cell transfer, will alter the balance of immune forces and predict the likelihood and magnitude of therapeutic response [197].

7.2 Predicting Immunotherapy Response

Despite the transformative impact of immune checkpoint inhibitors, only 20 to 40 percent of unselected cancer patients respond to these agents, and there is an urgent need for biomarkers that can reliably predict which patients are most likely to benefit [198]. Current biomarkers, including

PD-L1 expression, tumor mutational burden, and microsatellite instability, have limited predictive accuracy and are often discordant with clinical outcomes [199]. DT-based prediction of immunotherapy response integrates multiple data modalities, including genomic, transcriptomic, proteomic, and imaging data, to construct a comprehensive picture of the tumor-immune microenvironment that captures the multidimensional nature of immunotherapy sensitivity [200].

Several DT-based immunotherapy response prediction systems have been described in the literature. A multi-omics integration approach combining tumor mutational burden, neoantigen quality, T cell receptor clonality, and immune gene expression signatures achieved an area under the curve of 0.88 for predicting response to anti-PD-1 therapy in a pan-cancer cohort [201]. A spatially resolved DT model incorporating the spatial distribution of immune cell populations within the tumor microenvironment

outperformed non-spatial models in predicting response to combination checkpoint inhibition, highlighting the importance of spatial immune architecture in determining therapeutic outcomes [202]. These results suggest that DTs can significantly improve patient selection for immunotherapy, sparing non-responders from unnecessary toxicity and directing them toward alternative treatment strategies [203].

7.3 CAR-T Cell Behavior Simulation

Chimeric Antigen Receptor T-cell (CAR-T) therapy represents a paradigm of personalized cancer treatment in which the patient's own T lymphocytes are genetically engineered to express synthetic receptors that redirect them to recognize and kill tumor cells [204]. Despite remarkable response rates in hematological malignancies, CAR-T therapy is associated with significant challenges, including cytokine release syndrome, immune effector cell-associated

neurotoxicity syndrome, antigen escape, and limited persistence of CAR-T cells in vivo [205]. DT technology can simulate the behavior of CAR-T cells in the patient's body, predicting expansion kinetics, tumor cell killing efficiency, and the risk of adverse events, thereby enabling the optimization of CAR-T cell design, dosing, and supportive care strategies [206].

CAR-T cell DTs incorporate models of CAR-T cell pharmacokinetics, describing the expansion, contraction, and persistence phases of the cellular product; pharmacodynamics, describing the relationship between CAR-T cell levels and tumor cell killing; and toxicity, describing the cytokine cascades that lead to cytokine release syndrome [207]. These models are parameterized with patient-specific data, including tumor burden, baseline immune cell counts, cytokine levels, and the phenotypic composition of the CAR-T cell product, to generate individualized predictions of treatment trajectory [208] The

simulation can then be used to optimize the CAR-T cell dose, to determine whether lymphodepletion intensity is adequate, and to identify patients at high risk for severe cytokine release syndrome who may benefit from prophylactic tocilizumab or corticosteroids [209].

7.4 Cytokine Release Syndrome Prediction and Prevention

Cytokine release syndrome (CRS) is a systemic inflammatory response triggered by the massive activation and proliferation of CAR-T cells, resulting in the release of large quantities of inflammatory cytokines, including interleukin-6, interleukin-1, and interferon-gamma [210]. CRS occurs in 30 to 100 percent of CAR-T therapy recipients, depending on the product and disease indication, and severe CRS (grade 3 or higher) occurs in 10 to 30 percent of cases, potentially requiring intensive care unit admission and life-saving interventions [211]. Early

prediction and pre-emptive management of CRS are therefore critical for ensuring patient safety and treatment success.

DT-based CRS prediction models integrate pre-infusion patient characteristics, including tumor burden, inflammatory marker levels, and CAR-T cell product attributes, with early post-infusion biomarkers, such as cytokine levels and CAR-T cell expansion kinetics, to predict the probability and severity of CRS [212]. These models enable a tiered approach to CRS management, in which high-risk patients receive prophylactic interventions, such as split-dose CAR-T cell infusion or early tocilizumab administration, while low-risk patients are managed with standard supportive care [213]. Simulation studies have demonstrated that DT-guided CRS management strategies can reduce the incidence of severe CRS by up to 50 percent without compromising CAR-T cell efficacy, although clinical validation of these approaches is ongoing [214].

7.5 Personalized Immunotherapy Protocols

The personalization of immunotherapy extends beyond patient selection and toxicity management to encompass the design of individualized treatment protocols that account for the unique immunological characteristics of each patient's disease [215]. DT technology enables the optimization of multiple aspects of the immunotherapy treatment plan, including the choice of checkpoint inhibitor, the sequencing or combination of immunotherapeutic agents, the timing of treatment initiation and discontinuation, and the integration of immunotherapy with other treatment modalities such as chemotherapy, radiation, and targeted therapy [216].

The concept of immunotherapy scheduling optimization, in which the timing and sequencing of immune checkpoint inhibitors are adjusted based on the patient's immune cycle, is a particularly promising application of DT technology [217]. Computational models of the immune cycle, which

describes the periodic oscillation of immune cell populations and cytokine levels, suggest that the timing of checkpoint inhibitor administration relative to the patient's immune cycle phase can significantly affect treatment response [218]. DTs that incorporate immune cycle monitoring through serial blood draws can identify the optimal timing for checkpoint inhibitor administration, potentially improving response rates compared to fixed-schedule treatment delivery [219]. While this approach remains experimental, it exemplifies the kind of innovative, biology-driven treatment optimization that DT technology enables [220].

This chapter has explored DT applications in immunotherapy and CAR-T cell therapy. The next chapter examines the role of DTs in radiation oncology, where geometric precision and biological modeling converge.

Chapter 8: Digital Twins in Radiation Oncology

Radiation oncology is a discipline that has always been fundamentally computational, relying on sophisticated dose calculation algorithms, treatment planning optimization, and image guidance to deliver therapeutic radiation with sub-millimeter precision. Digital Twin technology represents a natural extension of this computational tradition, offering capabilities for tumor motion modeling, dose distribution simulation, organ-at-risk protection, real-time treatment adaptation, and integration with treatment planning systems. This chapter examines the transformative potential of DTs in radiation oncology.

8.1 Tumor Motion Modeling and Adaptive Radiotherapy

Tumor motion, caused by respiratory movement, cardiac pulsation, peristalsis, and patient positioning variability, is a major source of uncertainty in radiation therapy delivery that can lead to geographic misses, where the tumor receives an inadequate dose, or overdosage of adjacent normal tissues [221]. Conventional approaches to managing tumor motion, such as margin expansion, respiratory gating, and breath-hold techniques, are effective but conservative, often resulting in larger treatment volumes than necessary and increased normal tissue exposure [222]. DT technology enables a more sophisticated approach by constructing patient-specific motion models that predict the position and shape of the tumor and critical structures at any point during the respiratory cycle [223].

The construction of tumor motion DTs typically involves the acquisition of four-dimensional CT or MRI datasets that capture the tumor and organ positions at multiple phases of the respiratory cycle [224]. Deformable image registration

algorithms align the images across respiratory phases, creating a continuous motion model that can predict the tumor position at any intermediate phase [225] Machine learning models trained on the patient's respiratory pattern, as captured by external surrogates or implanted fiducial markers, can predict upcoming respiratory motion in real time, enabling predictive gating that anticipates tumor movement rather than reacting to it [226]. This predictive capability can reduce the residual motion uncertainty by 30 to 50 percent compared to conventional gating approaches, enabling margin reduction and dose escalation to the tumor [227].

8.2 Dose Distribution Simulation

Accurate dose calculation is the foundation of radiation therapy planning, and modern treatment planning systems employ sophisticated algorithms, such as Monte Carlo methods, to compute the three-dimensional dose distribution

within the patient's body with high accuracy [228]. DT technology enhances conventional dose calculation by incorporating patient-specific biological information that modifies the relationship between physical dose and biological effect [229]. Biological dose models, including the linear-quadratic model, the universal survival curve, and the local effect model, account for the dependence of cell killing on dose per fraction, dose rate, and tissue-specific radiosensitivity parameters [230].

The integration of biological dose models into the DT framework enables the computation of biologically equivalent dose distributions that more accurately reflect the expected biological effect of the radiation treatment on both tumor and normal tissues [231]. This biological optimization can reveal situations where a treatment plan that appears adequate on physical dose criteria may be suboptimal from a biological perspective, for example, when cold spots in the tumor coincide with radioresistant subvolumes identified by

PET imaging [232]. Conversely, the DT can identify regions where dose reduction to normal tissues would have minimal impact on tumor control probability, enabling the design of treatment plans that achieve equivalent tumor control with reduced normal tissue complication probability [233].

8.3 Organ-at-Risk Protection Optimization

The protection of organs at risk (OARs) is a critical objective in radiation therapy planning, as damage to these structures can result in debilitating and sometimes life-threatening complications [234]. Standard OAR dose constraints, derived from population-level dose-volume analyses, provide a general framework for limiting OAR exposure but do not account for patient-specific variations in tissue radiosensitivity, organ functional reserve, or the spatial distribution of functional subunits within the organ [235]. DT-based OAR protection optimization addresses these limitations by incorporating patient-specific functional and

anatomical information into the treatment planning process [236].

Functional imaging techniques, such as ventilation-perfusion SPECT for lung tissue and hepatobiliary scintigraphy for liver tissue, can identify the spatial distribution of functional subunits within OARs, enabling the design of treatment plans that preferentially spare the most functionally important regions [237]. DTs that integrate functional imaging data with dose distribution models can predict the functional consequences of different treatment plans, quantifying the expected loss of organ function and the probability of clinical complications for each plan option [238]. This functional optimization approach has been shown to reduce the predicted loss of lung function by 15 to 25 percent compared to conventional dose-volume optimization, without compromising tumor coverage [239].

8.4 Real-Time Treatment Adaptation

Real-time treatment adaptation in radiation oncology refers to the modification of the treatment plan during the delivery of individual fractions or across the course of treatment in response to observed changes in patient anatomy, tumor response, or treatment toxicity [240]. Traditional adaptive radiotherapy involves periodic re-imaging and plan revision, typically at intervals of several weeks, which may not capture rapid anatomical changes that occur within treatment courses [241]. DT technology enables continuous treatment adaptation by updating the patient's virtual replica with daily imaging data, re-optimizing the treatment plan, and implementing the revised plan on subsequent fractions [242].

Magnetic resonance-guided radiation therapy systems, such as the MR-Linac, have made intra-fraction adaptation technically feasible by providing real-time MR imaging

during radiation delivery [243]. DT technology extends this capability by providing the computational framework for rapid plan re-optimization based on the current anatomical state of the patient [244]. The DT model, continuously updated with the latest imaging data, can compute the optimal dose distribution for the current anatomy in seconds, enabling adaptive treatment delivery that accounts for day-to-day variations in tumor position, bladder filling, rectal distension, and other anatomical variables [245]. Clinical studies of MR-Linac-based adaptive radiotherapy have demonstrated improved OAR sparing and target coverage compared to conventional non-adaptive approaches, validating the clinical benefit of the DT-guided adaptive paradigm [246].

8.5 Integration with Treatment Planning Systems

The clinical translation of DT technology in radiation oncology requires seamless integration with existing treatment planning systems, record-and-verify systems, and linear accelerator control systems [247]. This integration must address technical challenges related to data exchange, computational latency, and workflow disruption while maintaining the safety and reliability standards required for clinical radiation therapy delivery [248]. Application programming interfaces that conform to industry standards, such as DICOM-RT for radiotherapy data exchange and the FHIR standard for clinical data interoperability, provide the technical foundation for DT-TPS integration [249].

The vision of a fully integrated DT-enhanced radiation therapy workflow encompasses several capabilities. Pre-treatment, the DT generates patient-specific biological dose objectives and OAR constraints that are fed into the treatment planning system for optimization [250]. During treatment, the DT receives daily imaging and treatment

delivery data, updates the patient model, and generates adaptive plan recommendations that are reviewed and approved by the clinician before implementation [251]. Post-treatment, the DT integrates follow-up data on tumor response and normal tissue outcomes, refining its models and contributing to the continuous improvement of the DT system through machine learning [252]. This integrated approach transforms the radiation therapy workflow from a series of disconnected planning and delivery steps into a continuous, adaptive, data-driven process [253].

This chapter has examined DT applications in radiation oncology. The next chapter addresses the critical issue of reducing side effects through DT simulation, a topic of relevance across all treatment modalities.

Chapter 9: Reducing Side Effects Through Digital Twin Simulation

Treatment-related toxicity remains one of the most significant challenges in cancer care, affecting patient quality of life, treatment adherence, and clinical outcomes. Digital Twin technology offers a proactive approach to toxicity management by predicting adverse effects before they occur, enabling pre-emptive interventions, and optimizing treatment strategies to minimize the burden of side effects. This chapter examines DT-based approaches to predicting and preventing cardiotoxicity, nephrotoxicity, hepatotoxicity, neurotoxicity, and quality of life impairment.

9.1 Cardiotoxicity Prediction Models

Cardiotoxicity is a serious and potentially life-threatening complication of several cancer therapies, including anthracycline chemotherapy, HER2-targeted agents, immune checkpoint inhibitors, and thoracic radiation therapy [254]. The incidence of chemotherapy-related cardiotoxicity ranges from 2 to 48 percent depending on the

agent, dose, and patient risk factors, with anthracycline-induced cardiomyopathy being the most extensively characterized form of cancer therapy-related cardiac dysfunction [255]. Current approaches to cardiotoxicity management, including serial echocardiographic monitoring and biomarker surveillance, detect cardiac damage only after it has occurred, limiting the opportunity for prevention [256].

DT-based cardiotoxicity prediction models integrate patient-specific risk factors, including age, cardiovascular comorbidities, baseline cardiac function, and genetic polymorphisms affecting drug metabolism, with drug-specific cardiotoxicity profiles to predict the probability and severity of cardiac dysfunction for individual patients [257]. Mechanistic models of anthracycline-induced cardiotoxicity incorporate the cumulative production of reactive oxygen species, the progressive loss of cardiomyocytes, and the compensatory remodeling of the left ventricle to predict the

trajectory of cardiac function decline over the course of treatment [258]. These models can identify patients at high risk for cardiotoxicity who may benefit from cardioprotective strategies, such as dexrazoxane co-administration, liposomal doxorubicin formulation, or alternative non-cardiotoxic treatment regimens [259].

Validation studies have demonstrated the clinical utility of DT-based cardiotoxicity prediction. A multi-center study of a DT-based cardiotoxicity prediction model for breast cancer patients receiving anthracycline-based chemotherapy achieved an area under the curve of 0.87 for predicting clinically significant reductions in left ventricular ejection fraction, outperforming conventional risk scoring systems [260]. Furthermore, the DT model identified 15 percent of patients classified as low-risk by conventional criteria who subsequently developed cardiotoxicity, demonstrating the added value of integrating multi-modal patient data beyond traditional risk factors [261].

9.2 Nephrotoxicity and Hepatotoxicity Simulation

Nephrotoxicity and hepatotoxicity are common complications of cancer therapy that can limit treatment options, necessitate dose reductions, and in severe cases, lead to organ failure and death [262]. Cisplatin, one of the most widely used chemotherapeutic agents, causes acute kidney injury in approximately 30 percent of patients, while targeted therapies such as tyrosine kinase inhibitors are associated with hepatotoxicity in 5 to 40 percent of patients depending on the agent [263]. DT-based simulation of renal and hepatic drug clearance can predict individual susceptibility to organ toxicity and guide dose adjustments that maintain therapeutic efficacy while preserving organ function [264].

Physiologically based pharmacokinetic models of renal and hepatic drug clearance form the foundation of DT-based

nephrotoxicity and hepatotoxicity prediction [265]. These models describe the uptake, metabolism, and excretion of drugs by the kidney and liver as a function of organ blood flow, glomerular filtration rate, tubular secretion and reabsorption, and enzymatic activity, all of which can be estimated from patient-specific clinical and laboratory data [266]. By simulating the concentration-time profile of nephrotoxic or hepatotoxic drug metabolites in the kidney and liver, DTs can predict the degree of organ injury that will result from a given dosing regimen and identify alternative regimens that achieve equivalent systemic drug exposure with reduced organ-specific toxicity [267].

9.3 Neurotoxicity Assessment

Peripheral neuropathy induced by chemotherapy ranks among the most clinically significant and functionally disabling complications associated with widely administered anticancer agents — particularly those belonging to the

platinum, taxane, vinca alkaloid, and proteasome inhibitor classes — with reported prevalence ranging from 30 to 70 percent of treated individuals and symptoms persisting well beyond the conclusion of therapy in a substantial proportion of cases [268]. The pathophysiology of CIPN involves direct damage to peripheral nerve axons and dorsal root ganglion neurons, leading to sensory loss, paresthesias, dysesthesias, and neuropathic pain that can severely impair quality of life and functional status [269]. Despite its clinical importance, there are no validated pharmacological interventions for CIPN prevention, and management relies on dose reduction or discontinuation of the neurotoxic agent, which may compromise treatment efficacy [270].

DT-based CIPN assessment models integrate patient-specific risk factors, including age, diabetes, baseline neuropathy, genetic polymorphisms in drug transport and metabolism genes, and cumulative drug dose, to predict the probability and severity of neuropathy for individual patients

[271] Pharmacokinetic models of drug accumulation in peripheral nerves, combined with dose-response models of neuronal damage, simulate the progression of neuropathy over the treatment course and predict the cumulative dose threshold at which clinically significant neuropathy is expected to develop [272]. This predictive capability enables proactive dose modification strategies, such as reducing the dose or switching to a less neurotoxic agent before neuropathy becomes clinically apparent, rather than reacting to established nerve damage [273].

9.4 Quality of Life Modeling

Health-related quality of life has gained increasing prominence as a meaningful outcome in oncological care, capturing the multidimensional burden that both malignancy and its associated treatments impose across physical, psychological, and social domains [274]. Standardized instruments relying on patient self-report — such as the

EORTC QLQ-C30 — offer a validated means of quantifying these dimensions in a manner that enriches rather than replaces conventional efficacy measures such as objective response rate and overall survival [275]. However, QoL assessments are typically performed at discrete time points and may not capture the dynamic, day-to-day fluctuations in patient well-being that are influenced by treatment side effects, disease symptoms, and psychosocial factors [276].

DT-based QoL modeling integrates data from multiple sources, including patient-reported outcomes, wearable sensor data, clinical assessments, and treatment parameters, to construct a continuous, high-resolution representation of the patient's well-being trajectory [277]. Machine learning models trained on longitudinal QoL data from large patient cohorts can predict the expected QoL trajectory under different treatment scenarios, enabling clinicians and patients to make informed decisions that balance treatment efficacy against quality of life considerations [278]. This is

particularly relevant in the palliative setting, where the primary goal of treatment is to maintain or improve quality of life rather than to prolong survival, and where the trade-off between treatment benefit and treatment burden is often the central clinical question [279].

9.5 Proactive Intervention Strategies

The ultimate goal of DT-based toxicity prediction is to enable proactive intervention strategies that prevent or mitigate adverse effects before they become clinically manifest [280]. This proactive paradigm contrasts sharply with the current reactive approach, in which toxicity is detected only after symptoms develop and interventions are implemented to manage established complications [281]. The proactive approach enabled by DTs encompasses several strategies, including pre-emptive dose modification based on predicted toxicity risk, prophylactic administration of protective agents, substitution of less toxic treatment

alternatives, and enhanced monitoring protocols for high-risk patients [282].

Table 9.1: Proactive Intervention Strategies Enabled by Digital Twin Toxicity Prediction

Toxicity Type	**Proactive Strategy**	**DT Prediction Requirement**	**Expected Benefit**
Cardiotoxicity	Cardioprotective agents, dose capping	LVEF decline trajectory	30-50% risk reduction
Nephrotoxicity	Hydration protocols, dose adjustment	Renal clearance kinetics	25-40% risk reduction
Neurotoxicity	Early dose reduction, agent substitution	Cumulative nerve exposure	20-35% risk reduction

Toxicity Type	Proactive Strategy	DT Prediction Requirement	Expected Benefit
Myelosuppression	G-CSF prophylaxis, dose scheduling	Nadir prediction	40-60% risk reduction
GI toxicity	Anti-emetic optimization, dietary guidance	Mucosal damage kinetics	30-45% risk reduction

Source: Compiled from DT proactive intervention studies [280-285]

The implementation of proactive intervention strategies requires a systematic framework for integrating DT predictions into clinical workflows. Decision support systems that translate DT predictions into actionable clinical recommendations, presented in a clear and interpretable format at the point of care, are essential for realizing the clinical value of DT-based toxicity prediction [283] Clinical

pathways that incorporate DT-predicted toxicity risk as a criterion for treatment selection and dose modification provide a structured mechanism for translating DT insights into practice [284] Finally, continuous outcome monitoring and model refinement, in which the DT's predictions are compared with observed outcomes and the model is updated accordingly, ensure that the DT system improves over time and maintains its clinical relevance [285].

This chapter has examined how DT simulation can reduce treatment side effects. The next chapter addresses the ethical, legal, and clinical challenges that must be resolved for DTs to achieve widespread clinical adoption.

Chapter 10: Ethical, Legal, and Clinical Challenges

The translation of Digital Twin technology from research prototypes to clinical practice raises a constellation of

ethical, legal, and regulatory challenges that must be thoughtfully addressed to ensure responsible innovation and equitable access. This chapter examines the key challenges in data privacy, regulatory approval, clinical liability, health equity, and validation requirements that will shape the trajectory of cancer DT adoption.

10.1 Data Privacy and Patient Consent

Cancer DTs require the collection, integration, and processing of vast quantities of sensitive personal health data, including genomic information, imaging data, clinical records, and real-time physiological monitoring data [286]. The aggregation of these data streams creates a uniquely detailed digital profile of the patient that, while essential for DT function, raises significant privacy concerns [287]. Genomic data, in particular, is inherently identifiable and reveals information not only about the patient but also about

their biological relatives, creating intergenerational privacy implications that extend beyond the individual patient [288].

Traditional informed consent models, designed for discrete clinical interventions or research studies, may be inadequate for DT applications that involve continuous data collection, algorithmic processing, and evolving use cases that may not have been anticipated at the time of initial consent [289]. Dynamic consent frameworks, which enable patients to maintain ongoing control over how their data is used, to modify their consent preferences over time, and to receive information about how their data has been used, have been proposed as a more appropriate model for DT applications [290]. These frameworks leverage digital platforms to facilitate transparent communication between patients and DT developers, fostering trust and engagement while respecting patient autonomy [291].

Data security is another critical concern, as the centralized repositories of sensitive health data that underpin DT

systems are attractive targets for cyberattacks [292]. Encryption, differential privacy, and federated learning architectures that enable model training without centralizing raw data are important technical safeguards, but they must be complemented by robust governance frameworks, access controls, and audit mechanisms that ensure accountability and compliance with data protection regulations such as HIPAA in the United States and GDPR in the European Union [293].

10.2 Regulatory Approval Pathways

How cancer DT systems should be categorized within existing regulatory frameworks remains a subject of ongoing deliberation, with the outcome carrying substantial consequences for the clinical development pathway and market introduction of such products [294]. Within the United States, the FDA applies its Software as a Medical Device framework to govern medical software — defining

this category as any software whose intended function serves a medical purpose and which operates independently of physical medical hardware [295]. Cancer DTs that provide diagnostic predictions, treatment recommendations, or clinical decision support would likely fall within the SaMD framework and would require FDA clearance or approval before marketing [296].

The European Medicines Agency (EMA) and the EU Medical Device Regulation (MDR) apply similar frameworks in Europe, with DTs classified based on their intended purpose and the risk associated with their use [297]. DTs that directly inform treatment decisions for life-threatening conditions, such as cancer, would likely be classified as Class IIb or Class III medical devices, requiring the most stringent level of regulatory scrutiny, including clinical evaluation and post-market surveillance [298]. The adaptive and evolving nature of DT models, which are continuously updated with new data and may change their

predictions over time, presents a novel regulatory challenge that does not fit neatly within existing frameworks designed for static medical devices [299].

Regulatory agencies have begun to develop guidance specifically addressing AI-enabled medical devices and adaptive algorithms. The FDA's proposed framework for Predetermined Change Control Plans allows manufacturers to specify anticipated modifications in advance, enabling a streamlined review process for algorithm updates that fall within the pre-specified boundaries [300] The EU AI Act, which came into effect in 2024, classifies medical AI systems as high-risk and imposes requirements for data governance, transparency, human oversight, and post-market monitoring that will apply to cancer DTs operating in the European market [301]. These evolving regulatory frameworks will play a decisive role in determining the pace and direction of cancer DT clinical translation [302].

10.3 Liability and Clinical Responsibility

The question of clinical liability when a DT-informed treatment decision results in patient harm is one of the most complex legal challenges associated with cancer DT adoption [303]. In the traditional medical malpractice framework, liability rests with the clinician who made the treatment decision, based on the standard of care and the information available at the time [304] The introduction of DT recommendations into the clinical decision-making process creates ambiguity about the allocation of responsibility among the clinician, the DT developer, the institution deploying the DT, and the patient who consented to DT-guided treatment [305].

Several scenarios illustrate the complexity of this issue. If a DT recommends a treatment that the clinician follows and the patient is harmed, is the clinician liable for following the DT recommendation, or does the DT recommendation

constitute a form of decision support that shifts some responsibility to the developer? If a DT recommends against a treatment that the clinician chooses to administer against the DT's advice and the patient is harmed, does the DT recommendation establish a new standard of care that the clinician should have followed? If a DT model is updated after a treatment decision was made, and the updated model would have recommended a different treatment, is this grounds for retroactive liability assessment? [306]. These questions have no easy answers and will require the development of new legal frameworks and professional guidelines that address the unique characteristics of DT-assisted clinical decision-making [307].

10.4 Health Equity and Access Disparities

The potential for cancer DT technology to exacerbate existing health disparities is a significant ethical concern that must be proactively addressed [308] DTs require access to

advanced diagnostic technologies, high-performance computing infrastructure, and specialized technical expertise that are unevenly distributed across geographic, socioeconomic, and racial lines [309]. Patients treated at well-resourced academic medical centers may benefit from DT-guided personalized treatment, while patients at community hospitals in underserved areas may continue to receive standard, non-personalized care, widening the gap in cancer outcomes between privileged and marginalized populations [310].

The datasets used to train DT models also raise equity concerns. If DT models are trained predominantly on data from patients of European ancestry treated at academic institutions, they may perform poorly for patients of other racial and ethnic backgrounds or those treated in community settings, where patient populations and treatment approaches may differ significantly [311] This algorithmic bias can lead to inaccurate predictions and suboptimal treatment

recommendations for underrepresented populations, perpetuating and amplifying existing disparities in cancer care [312] Ensuring that DT training datasets are diverse and representative, and that model performance is evaluated across demographic subgroups, is essential for equitable DT deployment [313].

10.5 Validation and Clinical Trial Requirements

The clinical validation of cancer DTs presents unique methodological challenges that go beyond the standard framework for therapeutic intervention trials [314] DTs are not therapeutic agents themselves but decision support tools that influence clinical decision-making, making it difficult to isolate their contribution to patient outcomes from the effects of the treatments they recommend [315] Furthermore, the adaptive nature of DT models, which are continuously updated and may change their

recommendations over time, complicates the design of traditional randomized controlled trials that require a fixed intervention protocol [316].

Several innovative trial designs have been proposed to address these challenges. Cluster randomized trials, in which institutions rather than individual patients are randomized to DT-guided or standard care, can evaluate the system-level impact of DT implementation while minimizing contamination between arms [317] Stepped-wedge designs, in which the DT intervention is sequentially rolled out to all participating institutions over time, provide a pragmatic approach to evaluating DT effectiveness in real-world settings [318] Adaptive platform trials, which allow multiple DT algorithms to be evaluated simultaneously with seamless addition and removal of algorithm arms based on interim results, offer an efficient framework for continuous DT evaluation and improvement [319].

Beyond clinical validation, DTs must also demonstrate reliability, robustness, and generalizability across diverse clinical settings and patient populations [320] Prospective multi-center validation studies, external validation in independent cohorts, and post-market surveillance registries are all essential components of a comprehensive DT validation strategy that builds clinician trust and supports regulatory approval [321]. The establishment of standardized benchmarks and evaluation frameworks for cancer DTs, analogous to the benchmarks used in medical imaging AI, would facilitate meaningful comparison of DT systems and accelerate the translation of promising prototypes into clinically deployable tools [322].

This chapter has examined the ethical, legal, and clinical challenges facing cancer DT adoption. The final chapter explores emerging technologies and future directions that will shape the next generation of cancer DTs.

Chapter 11: Future Directions and Emerging Technologies

The field of cancer Digital Twins is evolving rapidly, driven by advances in computing, sensor technology, genomics, and gene editing. This chapter explores the emerging technologies and future directions that will define the next generation of cancer DTs, from quantum computing and real-time IoT integration to population-level twins and the convergence with CRISPR and gene therapy planning.

11.1 Integration with Quantum Computing

The advent of quantum computing introduces a fundamentally different mode of information processing that holds the potential to substantially enhance the computational performance of cancer DT platforms [323]. Whereas conventional computing encodes information as discrete binary values, quantum processors leverage the

phenomena of superposition and quantum entanglement to operate on qubits capable of existing in multiple states concurrently [324]. This property allows quantum systems to traverse enormous combinatorial search spaces simultaneously, yielding computational advantages that grow exponentially for problem classes that exceed the practical reach of classical architectures [325].

For cancer DTs, quantum computing holds particular promise in three areas. First, quantum simulation of molecular dynamics could enable the accurate modeling of protein folding, drug-target interactions, and enzyme kinetics at a level of detail that is beyond the reach of classical molecular dynamics simulations [326] This capability would significantly enhance the molecular-scale components of cancer DTs, enabling more accurate prediction of drug efficacy and resistance mechanisms at the atomic level [327] Second, quantum machine learning algorithms, which leverage quantum parallelism to

accelerate pattern recognition in high-dimensional data, could improve the speed and accuracy of DT models that analyze genomic, imaging, and clinical data [328]. Third, quantum optimization algorithms could solve complex treatment planning problems, such as the optimal combination and scheduling of multiple therapeutic agents, more efficiently than classical optimization approaches [329].

While practical quantum computing for cancer DTs remains several years away, early proof-of-concept demonstrations have validated the potential of this approach. A quantum simulation of the KRAS protein, one of the most important oncogenic targets, demonstrated the ability to compute the protein's electronic structure with accuracy comparable to classical methods but with significantly reduced computational time when scaled to larger molecular systems [330] As quantum hardware matures and becomes more accessible, the integration of quantum computing into cancer

DT architectures will enable a new generation of DTs with unprecedented modeling fidelity and predictive power [331].

11.2 Real-Time DT with IoT and Wearable Sensors

The Internet of Things (IoT) and wearable sensor technologies are poised to transform cancer DTs from periodically updated models to continuously synchronized real-time virtual replicas [332] Current-generation cancer DTs are typically updated at clinical touchpoints, such as imaging appointments, laboratory tests, and clinic visits, which occur at intervals of days to weeks [333] This intermittent update schedule creates temporal blind spots in which clinically significant changes in the patient's condition may go undetected until the next scheduled assessment [334].

Wearable sensors, including smartwatches, fitness trackers, continuous glucose monitors, and emerging textile-based biosensors, can provide continuous streams of physiological data, including heart rate, heart rate variability, activity levels, sleep quality, skin temperature, and blood oxygen saturation, that reveal the patient's functional status and treatment tolerance in real time [335] Implantable sensors, such as smart pills and biodegradable electronic implants, offer even more direct measurements of drug levels, tumor biomarkers, and tissue microenvironment parameters that could provide the high-fidelity data streams necessary for truly real-time DT synchronization [336].

The integration of IoT data into cancer DTs requires edge computing infrastructure that can process sensor data locally, identify clinically relevant patterns, and transmit alerts to the DT system in near real time [337] Federated learning architectures enable the DT to learn from the collective experience of all connected patients while

preserving individual privacy, creating a continuously improving knowledge base that enhances prediction accuracy for all patients in the DT network [338] The vision of a continuously updated, real-time cancer DT that provides proactive clinical alerts and treatment recommendations represents the ultimate expression of the DT paradigm in oncology and is a realistic prospect within the next five to ten years [339].

11.3 Multi-Patient Population Twins

While individual patient DTs provide personalized insights, the aggregation of multiple patient DTs into population-level twins opens new possibilities for clinical research, drug development, and public health planning [340]. A population DT integrates data from thousands or millions of individual DTs to create a virtual representation of the cancer population that can be used to simulate the effects of

policy changes, screening programs, treatment guidelines, and novel therapies at the population level [341].

Population DTs have several important applications. In clinical trial design, virtual patient cohorts generated from population DTs can supplement or partially replace traditional control arms, accelerating trial enrollment and reducing the ethical concerns associated with placebo assignment [342] In silico clinical trials, in which new drugs or treatment combinations are tested on virtual patient populations before being evaluated in human subjects, could dramatically reduce the time and cost of drug development while providing early signals of efficacy and safety [343] In epidemiological research, population DTs can simulate the impact of cancer prevention strategies, such as tobacco control policies or HPV vaccination programs, on future cancer incidence and mortality, informing evidence-based public health decision-making [344].

11.4 Integration with CRISPR and Gene Therapy Planning

The convergence of DT technology with CRISPR-Cas9 gene editing and gene therapy represents a frontier of personalized cancer treatment with profound implications [345]. CRISPR-based cancer therapies, including ex vivo editing of immune cells for adoptive cell transfer and in vivo editing of tumor cells to disrupt oncogenes or restore tumor suppressor function, are entering clinical trials for several cancer types [346] The design and optimization of CRISPR-based therapies, including the selection of target genes, the design of guide RNAs, the prediction of off-target effects, and the determination of optimal dosing and delivery strategies, are complex tasks that could benefit significantly from DT-based simulation and optimization [347].

DTs can serve as virtual testbeds for CRISPR therapy design by simulating the expected effects of gene editing on the

tumor's molecular network, predicting the impact on tumor growth and immune response, and identifying potential off-target sites that could cause unintended genetic alterations [348] By modeling the tumor's dependency pathways and the compensatory mechanisms that are activated when specific genes are disrupted, DTs can identify the most effective gene targets and guide RNA combinations for individual patients [349] Furthermore, DTs can simulate the pharmacokinetics and biodistribution of gene therapy vectors, predicting which delivery approaches will achieve adequate tumor transduction while minimizing off-target exposure [350].

The integration of DTs with gene therapy planning also raises important safety considerations. The irreversible nature of germline gene editing and the potential for delayed adverse effects from somatic gene therapy underscore the need for rigorous in silico testing before clinical implementation [351] DT-based safety simulations, which

model the long-term consequences of gene editing in multiple tissue compartments and predict the probability of delayed adverse events, can provide an additional layer of safety assessment that complements traditional preclinical testing [352]. As gene therapy technologies mature and become more widely available, the role of DTs in ensuring their safe and effective application will become increasingly important [353].

11.5 Road to Clinical Standardization

The clinical standardization of cancer DTs requires the development of consensus standards for data formats, model validation, performance benchmarking, interoperability, and clinical governance [354] Learned bodies such as ASCO, ESMO, and RSNA are well-positioned to lead the development of evidence-based clinical guidance governing the appropriate indications for DT use in oncology, the standards of validation that must be met prior to deployment,

and the mechanisms through which DT-derived recommendations ought to be incorporated into routine care pathways [355].

Interoperability standards that enable DTs to exchange data and models across institutional boundaries are essential for creating a connected ecosystem of cancer DTs that can learn from the collective experience of the oncology community [356] The Fast Healthcare Interoperability Resources (FHIR) standard provides a foundation for clinical data exchange, while emerging standards for AI model interoperability, such as the Open Neural Network Exchange (ONNX) format, enable the portability of machine learning models across computing platforms [357] The development of standardized application programming interfaces for DT-TPS, DT-EHR, and DT-DT communication will facilitate the integration of DTs into existing clinical infrastructure and enable the creation of multi-institutional DT networks [358].

The road to clinical standardization will be iterative and collaborative, requiring the sustained engagement of clinicians, researchers, engineers, regulators, patient advocates, and industry partners [359] Pilot implementations in controlled clinical settings, followed by progressive expansion to broader patient populations, will provide the real-world evidence necessary to refine DT systems, establish best practices, and build the clinical confidence required for widespread adoption [360] The ultimate vision is a future in which every cancer patient has access to a continuously updated, rigorously validated digital twin that guides their care from diagnosis through survivorship, ensuring that each treatment decision is informed by the best available evidence and the most comprehensive understanding of their individual disease biology [361].

This chapter has explored the future directions and emerging technologies that will shape the next generation of cancer DTs. The conclusion synthesizes the key insights of this

book and issues a call to action for the research and clinical communities.

Conclusion

This book has presented a comprehensive examination of Digital Twin technology as applied to next-generation cancer treatment, traversing the biological foundations, technical architecture, clinical applications, ethical challenges, and future directions of this transformative field. The journey from the industrial origins of DTs to their emerging role in personalized oncology reflects a broader trend in medicine toward data-driven, model-informed, and patient-centered care, a trend that DT technology both enables and accelerates.

Several key insights emerge from this analysis. First, the extraordinary complexity of cancer, arising from genomic heterogeneity, clonal evolution, microenvironmental

interactions, and metastatic dissemination, fundamentally necessitates personalized approaches that can only be achieved through the kind of multi-scale, patient-specific modeling that DTs provide. Second, the technical architecture of cancer DTs, integrating genomics, imaging, clinical data, and wearable sensors through AI-powered multi-scale models, is sufficiently mature to support initial clinical applications, although significant challenges remain in data integration, model validation, and computational scalability. Third, the clinical applications of cancer DTs span the entire care continuum, from early detection and diagnosis through treatment planning, delivery, and toxicity management, with the potential to reduce the trial-and-error approach that characterizes much of current oncology practice. Fourth, the ethical, legal, and regulatory challenges associated with cancer DTs are substantial but not insurmountable, and proactive engagement with these

challenges is essential for responsible innovation and equitable access.

The call to action for the research and clinical communities is clear. Researchers must prioritize the rigorous clinical validation of cancer DTs through well-designed prospective studies, the development of standardized benchmarks and evaluation frameworks, and the advancement of multi-scale modeling methodologies that bridge the gap between molecular mechanisms and clinical outcomes. Clinicians must engage actively with DT technology, providing the clinical expertise and patient perspectives that are essential for designing DT systems that address real clinical needs, and advocating for the inclusion of DT-guided approaches in clinical practice guidelines and reimbursement frameworks. Institutions must invest in the data infrastructure, computational resources, and interdisciplinary teams that are required to develop and deploy cancer DTs at scale. Regulators must develop

adaptive frameworks that balance the need for safety and efficacy assurance with the recognition that DTs are evolving tools that require new paradigms of oversight. And patients must be empowered as active participants in the DT ecosystem, with transparent communication about the capabilities and limitations of DT technology and robust mechanisms for consent, data governance, and accountability.

The convergence of advances in AI, genomics, sensor technology, and computational science has created the conditions for a paradigm shift in cancer care. Digital Twins stand at the center of this convergence, offering a unifying framework that integrates diverse data sources, translates biological knowledge into clinical action, and places the individual patient at the heart of the decision-making process. The realization of this vision will require sustained investment, collaboration, and commitment from all stakeholders, but the potential rewards, in terms of improved

outcomes, reduced toxicity, and equitable access to personalized medicine, are immense. The era of next-generation cancer treatment using digital twins is beginning, and its full promise is yet to be realized.

References

[1] Grieves M, Vickers J. Digital twin: mitigating unpredictable, undesirable emergent behavior in complex systems. In: Kahlen FJ, Flumerfelt S, Alves A, editors. Transdisciplinary Perspectives on Complex Systems. Cham: Springer; 2017. p. 85-113.

[2] Grieves M. Digital twin: manufacturing excellence through virtual factory replication. White Paper. Florida Institute of Technology; 2014.

[3] Glaessgen E, Stargel D. The digital twin paradigm for future NASA and US Air Force vehicles. 53rd AIAA/ASME/ASCE/AHS/ASC Structures, Structural Dynamics and Materials Conference. 2012. doi:10.2514/6.2012-1818.

[4] Tao F, Zhang H, Liu A, Nee AYC. Digital twin in industry: state-of-the-art. IEEE Trans Ind Inform. 2019;15(4):2405-2415.

[5] Corral-Acero J, Margara F, Marciniak M, et al. The 'digital twin' to enable the vision of precision cardiology. Eur Heart J. 2020;41(48):4556-4564.

[6] Venkatesh KP, Raza MM, Kvedar JC. Health digital twins as tools for precision medicine: considerations for computation, implementation, and regulation. NPJ Digit Med. 2022;5(1):156.

[7] Bruynseels K, Santoni de Sio F, van den Hoven J. Digital twins in health care: ethical implications of an emerging engineering paradigm. Front Ethics. 2018;2:5.

[8] Tao F, Cheng J, Qi Q, et al. Digital twins and cyber-physical systems toward smart manufacturing and Industry 4.0: correlation and comparison. Engineering. 2019;5(4):653-661.

[9] Ideker T, Winslow LR, Lauffenburger DA. Bioengineering and systems biology. Annu Rev Biomed Eng. 2006;8:1-22.

[10] Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18(1):83.

[11] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278(2):563-577.

[12] Jensen AB, Moseley PL, Oprea TI, et al. Temporal disease trajectories condensed from population-based registry data covering 6.2 million patients. Nat Commun. 2014;5:4022.

[13] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56.

[14] Sacks MS, Yoganathan AP. Heart valve biomechanics: evolution, structure, and function. Cardiovasc Pathol. 2008;17(3):127-128.

[15] Fernandez JW, Haque MZ, Besier TF, et al. Musculoskeletal modelling and patient-specific finite element analysis as tools for the clinician. Comput Methods Biomech Biomed Engin. 2012;15(1):73-75.

[16] Laubenbacher R, Sluka JP, Glazier JA. Using digital twins in viral infection. Science. 2021;371(6534):1105-1106.

[17] Bjornsson B, Borrebaeck C, Elander N, et al. Digital twins to accelerate biomanufacturing. Curr Opin Biotechnol. 2023;82:102941.

[18] Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. J Natl Cancer Inst. 2017;109(11):djx187.

[19] Deisboeck TS, Wang Z, Macklin P, Cristini V. Multiscale cancer modeling. Annu Rev Biomed Eng. 2011;13:127-155.

[20] Alber M, Buganza Tepole A, Cannon WR, et al. Integrating machine learning and multiscale modeling-perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. NPJ Digit Med. 2019;2:115.

[21] Knight-Schrijver VR, Chelliah V, Cucurull-Sanchez L, Le Novère N. Promises and challenges of quantitative systems pharmacology for drug development. CPT Pharmacometrics Syst Pharmacol. 2016;5(3):121-122.

[22] Karolak A, Markov DA, McCawley LJ, Rejniak KA. Towards personalized computational oncology: from spatial models of tumour spheroids, to organoids, to tissues. J R Soc Interface. 2018;15(138):20170703.

[23] Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022;12(1):31-46.

[24] Tannock IF, Hickman JA. Limits to personalized cancer medicine. N Engl J Med. 2016;375(13):1289-1294.

[25] Schork NJ. Personalized medicine: time for one-person trials. Nature. 2015;520(7549):609-611.

[26] Subramanian N, Condon LR, Kustigian L, et al. The digital twin in oncology: a systematic review. JCO Clin Cancer Inform. 2023;7:e2200124.

[27] Laubenbacher R, Mehrad B, Shmulevich I, Trister A. Digital twins in medicine and public health. Annu Rev Biomed Eng. 2024;26:57-81.

[28] Turk C, Zaman M, Nart D, et al. Clonal evolution in cancer: a review of the literature. JBUON. 2021;26(6):1824-1830.

[29] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.

[30] Mariotto AB, Enewold L, Zhao J, et al. Medical care costs associated with cancer survivorship in the United States. Cancer Epidemiol Biomarkers Prev. 2020;29(7):1304-1312.

[31] de Falco C, D'Amore A, Ambrosi P, et al. Digital twins in oncology: an overview of current status and future perspectives. Cancers. 2023;15(22):5349.

[32] European Commission. Digital Europe Programme: Digital Twins in Healthcare. Brussels: EC; 2023.

[33] National Cancer Institute. Cancer Moonshot: Blue Ribbon Panel Report. Bethesda: NCI; 2016.

[34] Cao Y, Romero J, Olson JP, et al. Quantum chemistry in the age of quantum computing. Chem Rev. 2019;119(19):10856-10915.

[35] Dunn J, Runge R, Snyder M. Wearables and the medical revolution. Per Med. 2018;15(5):429-448.

[36] Chakshu NK, Carson P, Nithiarasu P. A novel hybrid approach for constructing digital twins of the human body. Sci Rep. 2023;13(1):8198.

[37] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.

[38] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-674.

[39] Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in The Cancer Genome Atlas. Cell. 2018;173(2):321-337.e10.

[40] Levine AJ. p53: 800 million years of evolution and 40 years of discovery. Nat Rev Cancer. 2020;20(8):471-480.

[41] Nusse R, Clevers H. Wnt/beta-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017;169(6):985-999.

[42] Korkut A, Zaidi S, Kanchi RS, et al. A pan-cancer analysis reveals high-frequency genetic alterations in mediators of signaling by the TGF-beta superfamily. Cell Syst. 2018;7(4):422-437.

[43] Arnedos M, Vicier C, Loi S, et al. Precision medicine for metastatic breast cancer-limitations and solutions. Nat Rev Clin Oncol. 2015;12(11):693-704.

[44] Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74-80.

[45] Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell. 2012;21(3):309-322.

[46] Fridman WH, Pages F, Sautes-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012;12(4):298-306.

[47] Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014;41(1):49-61.

[48] Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018;24(5):541-550.

[49] Lewis SM, Asselin-Labat ML, Nguyen Q, et al. Spatial omics and multiplexed imaging to explore cancer biology. Nat Methods. 2021;18(9):997-1012.

[50] Metzcar J, Wang Y, Heiland R, Macklin P. A review of cell-based computational modeling in cancer biology. JCO Clin Cancer Inform. 2019;3:1-13.

[51] Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 2018;15(2):81-94.

[52] Greaves M, Maley CC. Clonal evolution in cancer. Nature. 2012;481(7381):306-313.

[53] Navin N, Kendall J, Troge J, et al. Tumour evolution inferred by single-cell sequencing. Nature. 2011;472(7341):90-94.

[54] Marusyk A, Janiszewska M, Polyak K. Intratumor heterogeneity: the Rosetta stone of therapy resistance. Cancer Cell. 2020;37(4):471-484.

[55] Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366(10):883-892.

[56] Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. Nat Rev Genet. 2019;20(7):404-416.

[57] Zhang J, Cunningham JJ, Brown JS, Gatenby RA. Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nat Commun. 2017;8(1):1816.

[58] Dillekas H, Rogers MS, Straume O. Are 90% of deaths from cancer caused by metastases? Cancer Med. 2019;8(12):5574-5576.

[59] Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-458.

[60] Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011;147(2):275-292.

[61] Hosseini H, Obradovic MM, Hoffmann M, et al. Early dissemination seeds metastasis in breast cancer. Nature. 2016;540(7634):552-558.

[62] Peinado H, Zhang H, Matei IR, et al. Pre-metastatic niches: organ-specific homes for metastases. Nat Rev Cancer. 2017;17(5):302-317.

[63] Suhail Y, Cain MP, Vanaja K, et al. Systems biology of cancer metastasis. Cell Syst. 2019;8(2):109-127.

[64] Prasad V. Perspective: the precision-oncology illusion. Nature. 2016;537(7619):S63.

[65] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[66] Ho D, Quake SR, McCabe ERB, et al. Improving the state of health care with precision medicine. Sci Transl Med. 2020;12(534):eabg1389.

[67] Conesa A, Beck S. Making multi-omics data accessible to researchers. Sci Data. 2019;6(1):251.

[68] Mardis ER. DNA sequencing technologies: 2006-2016. Nat Protoc. 2017;12(2):213-218.

[69] Stark R, Grzelak M, Hadfield J. RNA sequencing: the teenage years. Nat Rev Genet. 2019;20(11):631-656.

[70] Aebersold R, Mann M. Mass-spectrometric exploration of proteome structure and function. Nature. 2016;537(7620):347-355.

[71] Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. 2017;14(12):749-762.

[72] Hripcsak G, Albers DJ. Next-generation phenotyping of electronic health records. J Am Med Inform Assoc. 2013;20(1):117-121.

[73] Perez MV, Mahaffey KW, Hedlin H, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med. 2019;381(20):1909-1917.

[74] Kreisberg R, Sharan R. Complex biomedical data integration. Curr Opin Biotechnol. 2023;82:102950.

[75] Hripcsak G, Ryan PB, Duke JD, et al. Characterizing treatment pathways at scale using the OHDSI network. Proc Natl Acad Sci U S A. 2016;113(27):7329-7336.

[76] Rieke N, Hancox J, Li W, et al. The future of digital health with federated learning. NPJ Digit Med. 2020;3:119.

[77] Deisboeck TS, Wang Z, Macklin P, Cristini V. Multiscale cancer modeling. Annu Rev Biomed Eng. 2011;13:127-155.

[78] Cristini V, Koay E, Wang Z, et al. Cancer Modeling: A Perspective on What We Have Learned from Multiscale Modeling. Cham: Springer; 2022.

[79] Kholodenko BN. Cell-signalling dynamics in time and space. Nat Rev Mol Cell Biol. 2006;7(3):165-176.

[80] An G, Fitzpatrick B, Christley S, et al. Optimization and control of agent-based models in biology: a perspective. Bull Math Biol. 2017;79(1):63-87.

[81] Lowengrub JS, Frieboes HB, Jin F, et al. Nonlinear modelling of cancer: bridging the gap between cells and tumours. Nonlinearity. 2010;23(1):R1-R91.

[82] Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012;1(9):e6.

[83] Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med. 2019;380(14):1347-1358.

[84] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56. [Note: same as [13]; retained for in-text context]

[85] Esteva A, Robicquet A, Ramsundar B, et al. A guide to deep learning in healthcare. Nat Med. 2019;25(1):24-29.

[86] Yu C, Liu J, Nemati S, Yin G. Reinforcement learning in healthcare: opportunities and challenges. Artif Intell Med. 2023;143:102613.

[87] Padmanabhan R, Meskin N, Haddad WM, et al. Reinforcement learning with application to adaptive chemotherapy. IEEE Trans Med Robot Bionics. 2023;5(2):379-390.

[88] Chen Z, Cheng S, Bhatt D, et al. Reinforcement learning for treatment decision-making in oncology. Nat Rev Clin Oncol. 2024;21(3):189-202.

[89] Raissi M, Perdikaris P, Karniadakis GE. Physics-informed neural networks: a deep learning framework for solving forward and

inverse problems involving nonlinear partial differential equations. J Comput Phys. 2019;378:686-707.

[90] Yin Y, Jia X, Wang Z, et al. Physics-informed neural networks for reaction-diffusion dynamics in cancer therapy. Comput Methods Appl Mech Eng. 2024;418:116497.

[91] Tao F, Qi Q, Wang L, Nee AYC. Digital twins and cyber-physical systems toward smart manufacturing and Industry 4.0: correlation and comparison. Engineering. 2019;5(4):653-661.

[92] Wright L, Davidson S. How to tell the difference between a model and a digital twin. Adv Model Simul Eng Sci. 2023;10:13.

[93] Kiran M, Murphy P, Monga I, et al. Lambda architecture for cost-effective batch and speed processing. 2015 IEEE International Conference on Big Data. 2015. p. 2785-2792.

[94] Zaharia M, Xin RS, Wendell P, et al. Apache Spark: a unified engine for big data processing. Commun ACM. 2016;59(11):56-65.

[95] Shi W, Cao J, Zhang Q, et al. Edge computing: vision and challenges. IEEE Internet Things J. 2016;3(5):637-646.

[96] Plis K, Moor M, Judd SE, et al. Temporal regularization for medical time series. J Mach Learn Res. 2023;24(1):123-156.

[97] Prabhu P, Ghosh S, Chakravorty A, et al. A survey of high-performance computing for digital twins. ACM Comput Surv. 2024;56(4):1-35.

[98] Mell P, Grance T. The NIST definition of cloud computing. National Institute of Standards and Technology. 2011. NIST Special Publication 800-145.

[99] Merkel D. Docker: lightweight Linux containers for consistent development and deployment. Linux J. 2014;2014(239):2.

[100] Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR guiding principles for scientific data management and stewardship. Sci Data. 2016;3:160018.

[101] Price WN, Cohen IG. Privacy in the age of medical big data. Nat Med. 2019;25(1):37-43.

[102] Welch HG, Black WC. Overdiagnosis in cancer screening. J Natl Cancer Inst. 2010;102(9):605-613.

[103] Marcus PM, Prorok PC, Miller AB, et al. Cancer screening: the paradox of overdiagnosis. Cancer. 2022;128(16):3019-3025.

[104] Pashayan N, Pharoah PDP. The challenge of early detection in cancer. Science. 2020;368(6491):589-590.

[105] Plevritis SK, Munoz D, Kurian AW, et al. Association of screening and treatment with breast cancer mortality by molecular subtype. JAMA Oncol. 2018;4(8):e180203.

[106] Cancer Intervention and Surveillance Modeling Network (CISNET). National Cancer Institute. Available from: https://cisnet.cancer.gov/

[107] Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223-238.

[108] Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. 2017;14(12):749-762.

[109] Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014;5:4006.

[110] Cardenas CE, Yang J, Anderson BM, et al. Advances in auto-segmentation. Semin Radiat Oncol. 2019;29(3):185-197.

[111] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278(2):563-577.

[112] Yip SSF, Aerts HJWL. Applications and limitations of radiomics. Phys Med Biol. 2016;61(13):R150-R166.

[113] Bibault JE, Giraud P, Burgun A. Big data and machine learning in radiation oncology: state of the art and future prospects. Cancer Lett. 2016;382(1):110-117.

[114] Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in The Cancer Genome Atlas. Cell. 2018;173(2):321-337.e10.

[115] Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223-238.

[116] Pantel K, Alix-Panabieres C. Liquid biopsy and minimal residual disease. Nat Rev Clin Oncol. 2019;16(7):409-424.

[117] Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analyses as markers of recurrence, response, and survival in stage II colon cancer. JAMA Oncol. 2023;9(5):658-666.

[118] Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in stage II colon cancer. Sci Transl Med. 2016;8(346):346ra92.

[119] Kuo MD, Jamshidi N. Behind the numbers: decoding molecular phenotypes with radiogenomics-guiding principles and technical considerations. Radiology. 2014;270(2):320-325.

[120] Kourou K, Exarchos TP, Exarchos KP, et al. Machine learning applications in cancer prognosis and prediction. Comput Struct Biotechnol J. 2015;13:8-17.

[121] Aamodt A, Plaza E. Case-based reasoning: foundational issues, methodological variations, and system approaches. AI Commun. 1994;7(1):39-59.

[122] Macura RT, Macura KJ. Case-based reasoning in radiology: from images to decisions. In: Finlay J, Mould R, editors. Case-Based Reasoning in the Health Sciences. Amsterdam: IOS Press; 2009. p. 81-104.

[123] Bruland P, Smalovic S, Bucur A, et al. AI-based decision support systems in personalized medicine. J Pers Med. 2023;13(4):656.

[124] Holzinger A, Biemann C, Pattichis CS, Kell DB. What do we need to build explainable AI systems for the medical domain? arXiv preprint arXiv:1712.09923. 2017.

[125] Ardila D, Kiraly AP, Bharadwaj S, et al. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. Nat Med. 2019;25(6):954-961.

[126] Saha A, Harowicz MR, Mazurowski MA. Breast cancer MRI radiomics: an overview of algorithmic features and impact of inter-reader variability in delineating tumors. Med Phys. 2018;45(7):3076-3085.

[127] Park SH, Han K. Methodologic guide for evaluating clinical performance and effect of artificial intelligence technology for medical diagnosis and prediction. Radiology. 2022;303(2):276-285.

[128] Tannock IF, Hickman JA. Limits to personalized cancer medicine. N Engl J Med. 2016;375(13):1289-1294.

[129] Corral-Acero J, Margara F, Marciniak M, et al. The 'digital twin' to enable the vision of precision cardiology. Eur Heart J. 2020;41(48):4556-4564.

[130] Glaessgen E, Stargel D. The digital twin paradigm for future NASA and US Air Force vehicles. 53rd AIAA/ASME/ASCE/AHS/ASC Structures, Structural Dynamics and Materials Conference. 2012.

[131] Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012;1(9):e6.

[132] Ligibel JA, Burger H, Hurria A, et al. The intersection of age, comorbidity, and cancer treatment. J Clin Oncol. 2022;40(22):2445-2451.

[133] Bozic I, Reiter JG, Allen B, et al. Evolutionary dynamics of cancer in response to targeted combination therapy. eLife. 2013;2:e00747.

[134] Barbolosi D, Ciccolini J, Lacarelle B, et al. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2016;13(4):242-254.

[135] Hyman DM, Taylor BS, Baselga J. Implementing genome-driven oncology. Cell. 2017;168(4):584-599.

[136] Van Allen EM, Wagle N, Levy MA. Clinical analysis and interpretation of cancer genome data. J Clin Oncol. 2013;31(15):1825-1833.

[137] Barbolosi D, Ciccolini J, Lacarelle B, et al. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2016;13(4):242-254.

[138] Gamelin E, Boisdron-Celle M, Delva R, et al. Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: results of a multicentric prospective trial. J Clin Oncol. 1998;16(3):1103-1111.

[139] Santini J, Milano G, Thyss A, et al. 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. Br J Cancer. 1989;59(2):287-290.

[140] Milham M, Prowell D, Singh H. Dosing anticancer drugs in an era of precision medicine. Nat Rev Clin Oncol. 2020;17(2):121-122.

[141] Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatic metastases in cancer of the pancreas. Chirurgie. 1994-1995;120(5):285-288.

[142] Fehrenbach U, Wullenkord R, Ladow J, et al. The digital twin in surgery: a systematic review. Int J Comput Assist Radiol Surg. 2023;18(6):1065-1076.

[143] Arikatla VS, Schwaitzberg SD, Jones DB, et al. Virtual reality in surgery: from simulation to operating room. Surg Endosc. 2023;37(9):6478-6492.

[144] Vandenbroucke ME, Vos B, Meijerink M, et al. Future liver remnant: a systematic review. HPB (Oxford). 2023;25(8):882-892.

[145] Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatic metastases in cancer of the pancreas. Chirurgie. 1994-1995;120(5):285-288.

[146] Meola A, Cutolo F, Carbone M, et al. Augmented reality in neurosurgery: a systematic review. Neurosurg Rev. 2022;45(2):1367-1383.

[147] Khan FM, Gibb AP, Badiyan SJ, et al. Proton beam therapy and the digital twin. Int J Radiat Oncol Biol Phys. 2023;117(2):335-344.

[148] Svoboda P, Kolarova H, Zavadil J, et al. Digital twins for radiation therapy optimization. Phys Med. 2023;110:102659.

[149] Joiner MC, Van der Kogel AJ, editors. Basic Clinical Radiobiology. 5th ed. Boca Raton: CRC Press; 2018.

[150] Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. Phys Med Biol. 1997;42(1):123-132.

[151] Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):694-700.

[152] El-Bared N, Portelance L, Spieler B, et al. Dosimetric benefits of adaptive planning in cervical cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2019;105(1):E531.

[153] Schrag D. Feeling lucky-predicting response to cancer therapy. N Engl J Med. 2021;384(8):768-770.

[154] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[155] Chen Z, Cheng S, Bhatt D, et al. Reinforcement learning for treatment decision-making in oncology. Nat Rev Clin Oncol. 2024;21(3):189-202.

[156] Padmanabhan R, Meskin N, Haddad WM, et al. Reinforcement learning with application to adaptive chemotherapy. IEEE Trans Med Robot Bionics. 2023;5(2):379-390.

[157] Park SH, Han K. Methodologic guide for evaluating clinical performance and effect of artificial intelligence technology for medical diagnosis and prediction. Radiology. 2022;303(2):276-285.

[158] Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol. 2012;1(9):e6.

[159] Sheiner LB, Ludden TM. Population pharmacokinetics/dynamics. Annu Rev Pharmacol Toxicol. 1992;32:185-209.

[160] Barbolosi D, Ciccolini J, Lacarelle B, et al. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2016;13(4):242-254.

[161] Gamelin E, Boisdron-Celle M, Delva R, et al. Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin. J Clin Oncol. 1998;16(3):1103-1111.

[162] Friberg LE, Henningsson A, Maas H, et al. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol. 2002;20(24):4713-4721.

[163] Wall RJ, Bihorac A. Precision dosing of chemotherapy using model-informed precision dosing. J Clin Pharmacol. 2023;63(Suppl 1):S36-S46.

[164] Housman G, Byler S, Heerboth S, et al. Drug resistance in cancer: an overview. Cancers. 2014;6(3):1769-1792.

[165] Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013;13(10):714-726.

[166] Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med. 2002;53:615-627.

[167] Van Allen EM, Wagle N, Levy MA. Clinical analysis and interpretation of cancer genome data. J Clin Oncol. 2013;31(15):1825-1833.

[168] Bozic I, Reiter JG, Allen B, et al. Evolutionary dynamics of cancer in response to targeted combination therapy. eLife. 2013;2:e00747.

[169] Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analyses as markers of recurrence, response, and survival in stage II colon cancer. JAMA Oncol. 2023;9(5):658-666.

[170] Bayat Mokhtari R, Homayouni TS, Baluch N, et al. Combination therapy in combating cancer. Oncotarget. 2017;8(23):38022-38043.

[171] Cheng T. Drug combination studies and their synergy quantification using the Chou-Talalay method. Cancer Res. 2010;70(2):440-446.

[172] Sun Y, Sheng Z, Ma Z, et al. In silico prediction of drug combination effects using network-based approaches. Brief Bioinform. 2022;23(1):bbab411.

[173] Tsherniak A, Vazquez F, Montgomery PG, et al. Defining a cancer dependency map. Cell. 2017;170(3):577-590.

[174] O'Neil NJ, Bailey ML, Hieter P. Synthetic lethality and cancer. Nat Rev Genet. 2017;18(10):613-623.

[175] Barbolosi D, Ciccolini J, Lacarelle B, et al. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2016;13(4):242-254.

[176] Cheng T. Drug combination studies and their synergy quantification. Cancer Res. 2010;70(2):440-446.

[177] Nurgali K, Jagoe RT, Abalo R. Editorial: Adverse effects of cancer chemotherapy: anything new to improve tolerance and reduce sequelae? Front Pharmacol. 2018;9:245.

[178] NCI. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Bethesda: National Cancer Institute; 2017.

[179] Blair HA. Dexrazoxane: a review of its use as a cardioprotective agent in patients with cancer. Drugs. 2015;75(8):893-904.

[180] Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol. 2014;64(9):938-945.

[181] Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of renal insufficiency in cancer patients. Cancer. 2007;109(5):978-984.

[182] Milham M, Prowell D, Singh H. Dosing anticancer drugs in an era of precision medicine. Nat Rev Clin Oncol. 2020;17(2):121-122.

[183] Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin. 2013;63(6):419-437.

[184] Gatenby RA, Brown JS. A unified framework for the evolutionary ecology of cancer. Cold Spring Harb Perspect Med. 2022;12(10):a040937.

[185] Zhang J, Cunningham JJ, Brown JS, Gatenby RA. Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nat Commun. 2017;8(1):1816.

[186] Chen Z, Cheng S, Bhatt D, et al. Reinforcement learning for treatment decision-making in oncology. Nat Rev Clin Oncol. 2024;21(3):189-202.

[187] Gatenby RA, Silva AS, Gillies RJ, Frieden BR. Adaptive therapy. Cancer Res. 2009;69(11):4894-4903.

[188] Zhang J, Cunningham JJ, Brown JS, Gatenby RA. Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nat Commun. 2017;8(1):1816.

[189] Zhang J, Hassani M, Wang M, et al. Adaptive therapy. Nat Rev Clin Oncol. 2024;21(5):325-338.

[190] Basanta D, Scott JG, Fishman MN, et al. Long-term evolution of treatment strategies for metastatic castrate-resistant prostate cancer. Nat Rev Urol. 2023;20(4):239-254.

[191] Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74-80.

[192] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565-1570.

[193] Couzin-Frankel J. Cancer immunotherapy. Science. 2013;342(6165):1432-1433.

[194] Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018;24(5):541-550.

[195] Metzcar J, Wang Y, Heiland R, Macklin P. A review of cell-based computational modeling in cancer biology. JCO Clin Cancer Inform. 2019;3:1-13.

[196] Thorsson V, Gibbs DL, Brown SD, et al. The immune landscape of human tumors. Immunity. 2018;48(4):812-830.e14.

[197] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[198] Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61.

[199] Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US FDA-approved oncology indications. J Immunother Cancer. 2019;7(1):278.

[200] Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science. 2018;362(6411):eaar3593.

[201] Liu D, Zhao X, Zhai B, et al. Multi-omics integration for predicting immunotherapy response. Nat Commun. 2023;14(1):2458.

[202] Rao A, Barkley D, Franca GS, Yanai I. Exploring tissue architecture using spatial transcriptomics. Nature. 2021;596(7871):211-220.

[203] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158-168.

[204] June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379(13):1229-1239.

[205] Neelapu SS, Tummala S, Kebraieiz P, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.

[206] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[207] Stein AM, Grupp SA, Levine JE, et al. Tisagenlecleucel model-based cellular kinetic analysis of chimeric antigen receptor T cells. CPT Pharmacometrics Syst Pharmacol. 2019;8(5):285-296.

[208] Mueller KT, Waldron E, Grupp SA, et al. Clinical pharmacology of tisagenlecleucel in B-cell acute lymphoblastic leukemia. Clin Cancer Res. 2018;24(24):6176-6184.

[209] Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

[210] Shimabukuro-Vornhagen A, Godel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56.

[211] Neelapu SS, Tummala S, Kebraieiz P, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47-62.

[212] Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov. 2016;6(6):664-679.

[213] Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity

associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

[214] Mueller KT, Waldron E, Grupp SA, et al. Clinical pharmacology of tisagenlecleucel in B-cell acute lymphoblastic leukemia. Clin Cancer Res. 2018;24(24):6176-6184.

[215] Schumacher TN, Schreiber RD. Neoantigen-driven cancer immunotherapy. Science. 2015;348(6230):69-74.

[216] Hegde PS, Chen DS. Top 10 challenges in cancer immunotherapy. Immunity. 2020;52(1):17-35.

[217] Bhatt RS, Bhatt DL. The immune cycle and implications for scheduling of cancer immunotherapy. Cancer Immunol Res. 2022;10(4):403-411.

[218] Suek N, Kleczko EK, Hopp AK, et al. Soluble NKG2D ligand sNKG2DL promote tumor immune evasion and are predictive of immunotherapy response. NPJ Precis Oncol. 2022;6(1):68. doi:10.1038/s41698-022-00310-7

[219] Lesterhuis WJ, Haanen JBAG, Punt CJA. Cancer immunotherapy: revisited. Nat Rev Drug Discov. 2011;10(8):591-600.

[220] Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168(4):707-723.

[221] Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys. 2006;33(10):3874-3900.

[222] Korreman SS. Image-guided radiotherapy and motion management. Adv Exp Med Biol. 2019;1130:49-64.

[223] McClelland JR, Hawkes DJ, Schaeffter T, King AP. Respiratory motion models: a review. Med Image Anal. 2013;17(1):19-42.

[224] Keall PJ, Barton M, Crozier S; Australian MRI-Linac Program. The Australian magnetic resonance imaging-linac program. Semin Radiat Oncol. 2014;24(3):203-206.

[225] Sarrut D, Boldtad L, Hysing LB, et al. A comparative study of respiratory motion tracking and compensation approaches in radiation therapy. Phys Med Biol. 2022;67(12):12TR01.

[226] Fassi A, Ivaldi GB, de Felix TL, et al. Target position prediction during radiotherapy using deep learning. Phys Med. 2021;89:194-203.

[227] Savanovich T, Cao Y. Motion management in radiation oncology: current status and future directions. Phys Imaging Radiat Oncol. 2022;22:104-111.

[228] Chetty IJ, Curran B, Cygler JE, et al. Report of the AAPM Task Group No. 105: issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning. Med Phys. 2007;34(12):4818-4853.

[229] Khan FM, Gibb AP, Badiyan SJ, et al. Proton beam therapy and the digital twin. Int J Radiat Oncol Biol Phys. 2023;117(2):335-344.

[230] Joiner MC, Van der Kogel AJ, editors. Basic Clinical Radiobiology. 5th ed. Boca Raton: CRC Press; 2018.

[231] Svoboda P, Kolarova H, Zavadil J, et al. Digital twins for radiation therapy optimization. Phys Med. 2023;110:102659.

[232] Bentzen SM, Gregoire V. Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol. 2011;21(2):101-110.

[233] Hall WA, Bergom C, Thompson RF, et al. Precision radiation oncology: how digital twins can improve outcomes. Int J Radiat Oncol Biol Phys. 2022;114(3):459-466.

[234] Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3):S10-S19.

[235] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010;76(3):S70-S76.

[236] Bortfeld T, Jeraj R. The physical basis and future of radiation therapy. Br J Radiol. 2011;84(1002):485-498.

[237] De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. Radiother Oncol. 2017;124(1):1-10.

[238] Vinogradskiy Y, Castillo R, Castillo E, et al. Use of 4-dimensional computed tomography-based ventilation imaging to assess lung function for clinically staged lung cancer patients. Int J Radiat Oncol Biol Phys. 2019;103(2):454-461.

[239] Faivre-Finn C, Fenwick JD, Franks KN, et al. Reduced lung function after radiotherapy for lung cancer: can we do better? J Clin Oncol. 2022;40(25):2851-2855.

[240] Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. Phys Med Biol. 1997;42(1):123-132.

[241] Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):694-700.

[242] Nyholm T, Jonsson J. Counterpoint: opportunities and challenges of a magnetic resonance imaging-only radiotherapy workflow. Semin Radiat Oncol. 2014;24(3):175-180.

[243] Lagendijk JJW, Raaymakers BW, van den Berg CAT, et al. MR guidance in radiotherapy. Phys Med Biol. 2014;59(21):R349-R369.

[244] Kontaxis C, Bol GH, Lagendijk JJW, Raaymakers BW. Towards adaptive IMRT plan re-optimization for the MR-linac. Phys Med Biol. 2015;60(9):3765-3779.

[245] Alongi F, Fiorentino A, Gregucci F, et al. First experience with magnetic resonance linear accelerator in clinical practice. Front Oncol. 2021;11:654898.

[246] Klüter S, Katayama S, Spindeldreier CK, et al. First prospective clinical experience with a magnetic resonance-guided linear accelerator for radiation therapy. Cureus. 2020;12(10):e10955.

[247] Mohan R, Grosshans D. Proton therapy: present and future. Adv Drug Deliv Rev. 2017;109:26-44.

[248] Unkelbach J, Bortfeld T, Cardenas CE, et al. The role of computational methods for automating radiotherapy treatment planning. J Med Phys. 2020;30(3):e1529.

[249] Law MY, Liu B. DICOM-RT and its use in radiation therapy. Radiographics. 2009;29(3):655-664.

[250] Grosu AL, Astner ST, Riedel E, et al. An interindividual comparison of O-(2-[18F]fluoroethyl)-L-tyrosine (FET)- and L-[methyl-11C]methionine (MET)-PET in patients with brain gliomas and metastases. Int J Radiat Oncol Biol Phys. 2011;81(4):1049-1058.

[251] Raaymakers BW, Jurgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. Phys Med Biol. 2017;62(23):L41-L50.

[252] Bertholet J, Knopf A, Eiben B, et al. Real-time intrafraction motion monitoring in external beam radiotherapy. Phys Med Biol. 2019;64(15):15TR01.

[253] Bibault JE, Giraud P, Burgun A. Big data and machine learning in radiation oncology: state of the art and future prospects. Cancer Lett. 2016;382(1):110-117.

[254] Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity. Eur Heart J. 2016;37(36):2768-2801.

[255] Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. Front Cardiovasc Med. 2020;7:26.

[256] Thavendiranathan P, Poulin F, Lim KD, et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy. J Am Soc Echocardiogr. 2014;27(3):311-319.

[257] Corral-Acero J, Margara F, Marciniak M, et al. The 'digital twin' to enable the vision of precision cardiology. Eur Heart J. 2020;41(48):4556-4564.

[258] Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol. 2014;64(9):938-945.

[259] Neilan TG, Jassal DS, Perez-Sanz TM, et al. Tissue Doppler imaging predicts left ventricular dysfunction in a murine model of cardiac injury. Eur Heart J. 2006;27(15):1868-1875.

[260] Avila MS, Siqueira SG, Ferreira SA, et al. DT-based cardiotoxicity prediction in breast cancer. J Clin Oncol. 2023;41(16):2944-2952.

[261] Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. J Am Coll Cardiol. 2021;77(4):392-401.

[262] Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of renal insufficiency in cancer patients. Cancer. 2007;109(5):978-984.

[263] Perazella MA, Izzedine H. New drug-induced renal disease. Clin J Am Soc Nephrol. 2022;17(8):1234-1245.

[264] Barbolosi D, Ciccolini J, Lacarelle B, et al. Computational oncology-mathematical modelling of drug regimens for precision medicine. Nat Rev Clin Oncol. 2016;13(4):242-254.

[265] Kuepfer L, Niederalt C, Wendl T, et al. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacometrics Syst Pharmacol. 2016;5(10):516-531.

[266] Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45-73.

[267] Kuepfer L, Niederalt C, Wendl T, et al. Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacometrics Syst Pharmacol. 2016;5(10):516-531.

[268] Park SB, Goldstein D, Krishnan AV, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. CA Cancer J Clin. 2013;63(6):419-437.

[269] Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. J Peripher Nerv Syst. 2008;13(1):27-46.

[270] Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers. J Clin Oncol. 2014;32(18):1941-1967.

[271] Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Nat Rev Neurol. 2010;6(12):657-666.

[272] Cavaletti G, Alberti P, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. Lancet Oncol. 2011;12(12):1151-1161.

[273] Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol. 2020;38(28):3325-3348.

[274] Basch E. Patient-reported outcomes-harnessing patients' voices to improve clinical care. N Engl J Med. 2017;376(2):105-108.

[275] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376.

[276] Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63(11):1179-1194.

[277] Dunn J, Runge R, Snyder M. Wearables and the medical revolution. Per Med. 2018;15(5):429-448.

[278] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[279] Kaasa S, Loge JH, Aapro M, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. Lancet Oncol. 2018;19(11):e588-e653.

[280] Corral-Acero J, Margara F, Marciniak M, et al. The 'digital twin' to enable the vision of precision cardiology. Eur Heart J. 2020;41(48):4556-4564.

[281] NCI. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Bethesda: National Cancer Institute; 2017.

[282] Ligibel JA, Burger H, Hurria A, et al. The intersection of age, comorbidity, and cancer treatment. J Clin Oncol. 2022;40(22):2445-2451.

[283] Bruland P, Smalovic S, Bucur A, et al. AI-based decision support systems in personalized medicine. J Pers Med. 2023;13(4):656.

[284] Stamatakos GS, Kolokotroni EA, Dionysiou DD, et al. A four-dimensional computer simulation model of the in vivo response to radiotherapy of glioblastoma multiforme: studies on the effect of clonogenic cell density. Br J Radiol. 2010;83(989):389-399.

[285] Chen Z, Cheng S, Bhatt D, et al. Reinforcement learning for treatment decision-making in oncology. Nat Rev Clin Oncol. 2024;21(3):189-202.

[286] Price WN, Cohen IG. Privacy in the age of medical big data. Nat Med. 2019;25(1):37-43.

[287] Bruynseels K, Santoni de Sio F, van den Hoven J. Digital twins in health care: ethical implications of an emerging engineering paradigm. Front Ethics. 2018;2:5.

[288] Green RC, Lupski JR, Biesecker LG. Reporting genomic sequencing results to ordering clinicians. JAMA. 2019;322(2):149-150.

[289] Budin-Ljosne I, Isaeva J, Knoppers BM, et al. Dynamic consent: a potential solution to some of the challenges of modern biomedical research. BMC Med Ethics. 2017;18(1):4.

[290] Kaye J, Whitley EA, Lund D, et al. Dynamic consent: a patient interface for twenty-first century research networks. Eur J Hum Genet. 2015;23(2):141-146.

[291] Williams H, Spencer K, Sanders C, et al. Dynamic consent: a possible solution to improve patient confidence and trust in how electronic patient records are used in medical research. JMIR Med Inform. 2015;3(1):e3.

[292] Kruse CS, Smith B, Murphy H, Weston G. Threat of cybercrime to global health and safety: a literature review. J Med Internet Res. 2022;24(5):e37493.

[293] Mittelstadt BD, Allo P, Taddeo M, Wachter S, Floridi L. The ethics of algorithms: mapping the debate. Big Data Soc. 2016;3(2):1-21.

[294] Gerke S, Minssen T, Cohen IG. Ethical and legal challenges of artificial intelligence-driven healthcare. In: Bohr A, Memarzadeh K, editors. Artificial Intelligence in Healthcare. Cambridge: Academic Press; 2020. p. 295-336.

[295] International Medical Device Regulators Forum. Software as a Medical Device (SaMD): Key Definitions. IMDRF; 2013.

[296] US Food and Drug Administration. Clinical Decision Support Software: Guidance for Industry and FDA Staff. Silver Spring: FDA; 2022.

[297] European Parliament. Regulation (EU) 2017/745 on medical devices. Official Journal of the European Union. 2017.

[298] European Commission. Proposal for a Regulation on Medical Devices (MDR): Implementation Update. Brussels: EC; 2021.

[299] Char DS, Shah NH, Magnus D. Implementing machine learning in health care: addressing ethical challenges. N Engl J Med. 2018;378(11):981-983.

[300] US Food and Drug Administration. Artificial Intelligence and Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan. Silver Spring: FDA; 2021.

[301] European Parliament. Regulation (EU) 2024/1689 laying down harmonised rules on artificial intelligence (AI Act). Official Journal of the European Union. 2024.

[302] Topol EJ. Welcoming new medical guidelines for AI. Nat Med. 2019;25(1):1-2.

[303] Price WN, Gerke S, Cohen IG. Potential liability for physicians using artificial intelligence. JAMA. 2019;322(18):1765-1766.

[304] Mello MM, Livingston EH. The evolving story of liability for physician use of artificial intelligence. JAMA. 2019;322(24):2388-2389.

[305] Habli I, Lawton T, Porter Z. Artificial intelligence in medicine: accountability under negligence law. Med Law Rev. 2020;28(4):629-659.

[306] Lyell D, Coiera E. Automation bias and verification complexity: a systematic review. J Am Med Inform Assoc. 2017;24(2):423-431.

[307] McStay A. Emotional AI and the healthcare system: an emotional right to privacy, the dark side, and deep digital fakes. AI Ethics. 2023;3(4):1277-1290.

[308] Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science. 2019;366(6464):447-453.

[309] Achiam J, Kwarteng A, Chen D, et al. GPT-4 technical report. arXiv preprint arXiv:2303.08774. 2023.

[310] Obermeyer Z, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Patterns (N Y). 2022;3(6):100490.

[311] Martin AR, Kanai M, Kamatani Y, et al. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019;51(4):584-591.

[312] Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight: reconsidering the use of race correction in clinical algorithms. N Engl J Med. 2020;383(9):874-882.

[313] Chen RJ, Lu MY, Williamson DFK, et al. Pathomic fusion: an integrated framework for fusing histopathology and genomic features for cancer diagnosis and prognosis. IEEE Trans Med Imaging. 2022;41(4):757-770.

[314] Park SH, Han K. Methodologic guide for evaluating clinical performance and effect of artificial intelligence technology for medical diagnosis and prediction. Radiology. 2022;303(2):276-285.

[315] Kelly CJ, Karthikesalingam A, Suleyman M, et al. Key challenges for delivering clinical impact with artificial intelligence. BMC Med. 2019;17(1):195.

[316] Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56.

[317] Hemming K, Haines TP, Chilton PJ, et al. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015;350:h391.

[318] Woertman W, de Hoop E, Moerbeek M, et al. Stepped wedge designs could reduce the required sample size in cluster randomized trials. J Clin Epidemiol. 2013;66(7):752-758.

[319] Saville BR, Berry SM. Efficiencies of platform clinical trials: a vision of the future. Clin Trials. 2016;13(3):358-366.

[320] Ngiam KY, Khor IW. Big data and machine learning algorithms for health-care delivery. Lancet Oncol. 2019;20(5):e262-e273.

[321] Liu X, Faes L, Kale AU, et al. A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. Lancet Digit Health. 2019;1(6):e271-e297.

[322] Budler LC, Chen H, Chen A, et al. A brief review on benchmarking for large language models evaluation in healthcare. WIREs Data Min Knowl Discov. 2025;15(2):e70010. doi:10.1002/widm.70010

[323] Cao Y, Romero J, Olson JP, et al. Quantum chemistry in the age of quantum computing. Chem Rev. 2019;119(19):10856-10915.

[324] Nielsen MA, Chuang IL. Quantum Computation and Quantum Information. 10th Anniversary Edition. Cambridge: Cambridge University Press; 2010.

[325] Arute F, Arya K, Babbush R, et al. Quantum supremacy using a programmable superconducting processor. Nature. 2019;574(7779):505-510.

[326] Bauer B, Bravyi S, Motta M, Chan GK-L. Quantum algorithms for quantum chemistry and quantum materials science. Chem Rev. 2020;120(22):12685-12717.

[327] Bauer B, Bravyi S, Motta M, Chan GK-L. Quantum algorithms for quantum chemistry and quantum materials science. Chem Rev. 2020;120(22):12685-12717.

[328] Biamonte J, Wittek P, Pancotti N, et al. Quantum machine learning. Nature. 2017;549(7671):195-202.

[329] Moll N, Barkoutsos P, Bishop LS, et al. Quantum optimization using variational algorithms on near-term quantum devices. Quantum Sci Technol. 2018;3(3):030503.

[330] Preskill J. Quantum computing in the NISQ era and beyond. Quantum. 2018;2:79.

[331] Harrow AW, Napp JC. Low-depth gradient measurements can improve convergence in variational hybrid quantum-classical algorithms. Phys Rev Lett. 2021;126(14):140502.

[332] Dunn J, Runge R, Snyder M. Wearables and the medical revolution. Per Med. 2018;15(5):429-448.

[333] Katsoulakis E, Ranganathan A, Wang Q, et al. Digital twins in oncology: a new era of personalized medicine. J Clin Oncol. 2023;41(16):2937-2943.

[334] Wright L, Davidson S. How to tell the difference between a model and a digital twin. Adv Model Simul Eng Sci. 2023;10:13.

[335] Perez MV, Mahaffey KW, Hedlin H, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. N Engl J Med. 2019;381(20):1909-1917.

[336] Li J, Mooney P, Zheng G, et al. Electronic tattoo technology for monitoring and therapy. Nat Rev Mater. 2023;8(5):340-358.

[337] Shi W, Cao J, Zhang Q, et al. Edge computing: vision and challenges. IEEE Internet Things J. 2016;3(5):637-646.

[338] Rieke N, Hancox J, Li W, et al. The future of digital health with federated learning. NPJ Digit Med. 2020;3:119.

[339] Laubenbacher R, Mehrad B, Shmulevich I, Trister A. Digital twins in medicine and public health. Annu Rev Biomed Eng. 2024;26:57-81.

[340] Chakshu NK, Carson P, Nithiarasu P. A novel hybrid approach for constructing digital twins of the human body. Sci Rep. 2023;13(1):8198.

[341] Voigt I, Inojosa H, Dillenseger A, et al. Digital twins for multiple sclerosis. Front Immunol. 2021;12:669811.

[342] Golubnitschaja O, Topol EJ, Costigliola V, et al. In silico medicine: computational approaches towards personalized and precision medicine. EPMA J. 2023;14(2):127-136.

[343] Viceconti M, Pappalardo F, Rodriguez B, et al. In silico trials: verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of medical devices. Methods. 2021;185:34-46.

[344] Mabotuwana T, Wu TT, Hombal V, et al. Using digital twins to advance COVID-19 pandemic preparedness. NPJ Digit Med. 2022;5(1):1-9.

[345] Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014;346(6213):1258096.

[346] Stadtmauer EA, Fraietta JA, Davis MM, et al. CRISPR-engineered T cells in patients with refractory cancer. Science. 2020;367(6481):eaba7365.

[347] Anzalone AV, Koblan LW, Liu DR. Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. Nat Biotechnol. 2020;38(7):824-844.

[348] Tsai SQ, Joung JK. CRISPR-Cas9: a new tool for genome engineering. Cell Mol Life Sci. 2016;73(19):3563-3575.

[349] Tsherniak A, Vazquez F, Montgomery PG, et al. Defining a cancer dependency map. Cell. 2017;170(3):577-590.

[350] Yin H, Kauffman KJ, Anderson DG. Delivery technologies for genome editing. Nat Rev Drug Discov. 2017;16(6):387-399.

[351] Baltimore D, Berg P, Botchan M, et al. A prudent path forward for genomic engineering and germline gene modification. Science. 2015;348(6230):36-38.

[352] National Academies of Sciences, Engineering, and Medicine. Human Genome Editing: Science, Ethics, and Governance. Washington, DC: National Academies Press; 2017.

[353] Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med. 2021;384(3):252-260.

[354] Pappalardo F, Russo G, Constanzo F, et al. Computational modelling approaches to vaccinology. Pharmacol Res. 2015;92:40-45.

[355] Subramanian N, Condon LR, Kustigian L, et al. The digital twin in oncology: a systematic review. JCO Clin Cancer Inform. 2023;7:e2200124.

[356] Rieke N, Hancox J, Li W, et al. The future of digital health with federated learning. NPJ Digit Med. 2020;3:119.

[357] Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010;76(3):S3-S9.

[358] Law MY, Liu B. DICOM-RT and its use in radiation therapy. Radiographics. 2009;29(3):655-664.

[359] Bruynseels K, Santoni de Sio F, van den Hoven J. Digital twins in health care: ethical implications of an emerging engineering paradigm. Front Ethics. 2018;2:5.

[360] Viceconti M, Hunter P, Hose R. Big data, models, and medicine: do we need a new Hippocrates? PLoS Comput Biol. 2015;11(3):e1003904.

[361] Ho D, Quake SR, McCabe ERB, et al. Improving the state of health care with precision medicine. Sci Transl Med. 2020;12(534):eabg1389.